SOME VIRUS ISOLATIONS FROM COMMON COLDS

I. EXPERIMENTS EMPLOYING HUMAN VOLUNTEERS

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WORK on the common cold is hampered because it has not been possible to detect or propagate the causative virus or viruses except by inoculation of human volunteers or chimpanzees. In this and the following papers we describe some properties of the cold viruses under study at this unit, and evidence for their transmission in vitro. The first paper lays particular emphasis on experiments employing human volunteers and the second and third on some laboratory studies. It should, however, be made clear that the various lines of work have been artificially separated and were actually carried on in parallel.

Clinical Methods

Volunteers were isolated and observed at this unit by the methods previously described (Andrewes 1949, Roden 1958). They were isolated for 4 days before administration of the inoculum and were observed for 5 days after inoculation. The inoculum of 1 ml., diluted if necessary in Hanks' saline, was administered as drops up the nostrils. Assessments were made by a clinical observer unaware of the nature of the material under test.

Laboratory Methods

Tissue-culture Techniques

Human embryos from therapeutic hysterotomies performed between 3 and 5 months of gestation were dissected aseptically at the Royal Marsden Hospital. The kidneys and lungs were placed in a sterile bottle immersed in broken ice and sent to this unit by train. The renal cortex and medulla were chopped with sharp scalpels into pieces about 1 mm. across and placed in Hanks' saline. The tissue was washed and the cells were dispersed by treatment with 0·25% 'Difco' trypsin in Hanks' saline at 37°C and a pH of about 7·4. The cell suspension was removed and added to 5 ml. horse serum and the process repeated. The cells were spun down and resuspended in medium to give a final dilution of 1/100 to 1/500. The medium consisted of 5% or 10% calf serum and 0·5% lact-albumin hydrolysate in Hanks' saline containing 0·03% sodium bicarbonate and 100 units penicillin, 100 μg. streptomycin, and 20 units of nystatin (mycostatin) per ml. 1 ml. was added to culture tubes closed with silicone bungs. The tubes were incubated at 37°C without rotation and the medium was renewed every 2 or 3 days until a cell sheet was formed; this usually took about 5 days.

Human embryo lung cultures were prepared in the same way. Human thyroid cultures were prepared as described by Pulvertaft et al. (1959), calf kidney cultures and monkey kidney cultures as described elsewhere (Negroni and Tyrrell 1959). When ready for use, the cultures were washed with Hanks' saline and 1·5 ml. of medium 199 with the antibiotics mentioned above was added. 0·2 ml. of inoculum was then added, and the cultures were placed in a roller drum.

The medium was usually changed 1 day after inoculation and at intervals of 4 days thereafter if necessary. Incubation at this stage was either at 33° or 36°C.

In early experiments it was thought that cold virus in the fluids from cultures maintained in medium 199 was losing its activity on storage or after repeated freezing and thawing; thereafter 0·5% of bovine plasma-albumin, fraction V (B.P.A.),* was added to culture fluids before storage in the dry-ice refrigerator, and specimens were frozen and thawed only once.

The Virus Strains

From adults, not in isolation, with typical common colds, nasal washings were taken, using either 10% broth saline or Hanks' saline containing 0·5% bovine plasma-albumin; 100 units of penicillin and 100 μg. of streptomycin per ml. were added. The washings were shaken with glass beads and centrifuged at about 2000 r.p.m. for 10 minutes. After 1/10 dilution in broth saline or Hanks' saline they produced typical colds when inoculated into volunteers.

To exclude the presence of known viruses the washings were then introduced into tissue cultures—in early experiments HeLa cell and human embryo lung cultures were used. Later we turned to cultures of human embryo kidney and monkey kidney cells maintained in medium 199 and tested for hæmadsorption (Vogel and Shelokov 1957). Several passages were made and the total period of observation was several weeks. We found no evidence of the presence of known enteroviruses, adenoviruses, or the parainfluenza (hæmadsorption) viruses recently isolated from persons with respiratory diseases (see reviews by Huebner et al. 1958 and Andrewes 1959). Washings were stored in a dry-ice refrigerator at about −50°C and thawed immediately before use.

Results

Properties of the Viruses

We made a few observations on properties of the agent producing colds in volunteers, for reasons which will become apparent later in this series.

(*a*) *Ether Resistance*

Washings were mixed with from 10 to 20% by volume of diethyl ether and held at 4°C overnight. The ether was then removed and the washings were inoculated into groups of volunteers. Control material was prepared in the same way without addition of ether. The virus apparently survived ether treatment in 5 of the 6 washings tested. In the case of the P.K. pool of washings, 5 of 14 volunteers inoculated with ether-treated material developed colds while 6 of 14 inoculated with untreated material did so. With H.G.P. washings, the corresponding figures were 1 of 6 and 1 of 5.

(*b*) *Acid Resistance*

A washing containing strain H.G.P. was dialysed at 4°C for 3 hours against 0·1 *M* citrate buffer pH 2·1; the buffer was then removed by dialysis against saline. None of 7 volunteers who received this material developed colds, although 2 of 8 volunteers who received untreated material did so.

(*c*) *Neutralisation by Human Serum*

The strain of H.G.P. was used for experiments to determine whether a virus of this type could be neutralised by immune

* Supplied by Armour Laboratories, Hampden Park, Eastbourne, England.

TABLE I—NEUTRALISATION IN VITRO OF COMMON COLD VIRUS (STRAIN H.G.P.)

—	No. of colds in volunteers receiving washing mixed with				
	Broth saline	Acute phase serum*	Convalescent serum*	Bovine plasma albumin	Human γ-globulin
Experiment I	3/8†	2/10	1/10	..	..
Experiment II	3/9	..	..	3/10	0/18

* The sera were obtained from subject H.G.P. at the time the washings were taken and 16 days later.
† Numerator = no. of colds. Denominator = number of volunteers inoculated.

serum. Acute and convalescent phase sera from the donor of the washings were heated at 56°C for 30 minutes, diluted 1 in 10, and mixed with an equal volume of washings diluted 1/5. The mixtures were held at room-temperature for about 2 hours before inoculation to volunteers. In a second experiment the washings were mixed with an equal volume of a solution of Lister Institute human γ-globulin 10 mg. per ml. and held at 4°C overnight and then at room temperature for 2 hours. A control containing bovine plasma-albumin was also used. The results are shown in table I. The serum did not neutralise the virus but the γ-globulin apparently did so. Since the bovine albumin did not neutralise, it is probable that the effect of the γ-globulin was due to its content of antibodies. The results and conclusions are similar to those of Jackson et al. (1958).

Propagation of Virus: Early Attempts

Andrewes et al. (1953) reported an apparently successful attempt to transmit a common cold strain (D.C.) in roller-tube cultures of human embryo lung maintained in Enders' medium. However, no colds were produced with material beyond the tenth passage and numerous attempts over 2 years to repeat the experiments were unsuccessful (Pereira and Roden, unpublished experiments). It seemed that some technical modification might hold the key to success. Accordingly the method of organ culture was used. No success was obtained using human embryonic œsophagus, skin, nasal epithelium, or intestine. There was rather more promise with fragments of embryonic human trachea (see Bang and Niven 1958). A few colds did occur in volunteers inoculated with the first passage in such cultures. The results were, however, irregular; colds could not be produced with material from passages beyond the first and it seems possible that the few colds were caused by virus surviving from the inoculum.

Further experiments with roller-tube cultures of monkey kidney were then carried out. We tried medium 199, Enders' medium (5% horse serum, 5% beef embryo extract, and 90% bovine amniotic fluid), and 0·1% yeast extract with 0·5% lactalbumin hydrolysate in Hanks' saline; and we varied the interval between passing. Colds occurred infrequently and irregularly in volunteers receiving material from any of these cultures.

An attempt was next made to repeat the experiment using human embryo kidney cultures. Because of shortage of materials only medium 199 was used and the experiment had to be discontinued as the cultures began to disintegrate after 10 days in this medium. Nevertheless material from these cultures produced colds in volunteers more frequently and the matter was therefore systematically investigated, as described below.

TABLE II—COLDS PRODUCED BY INOCULATION OF VOLUNTEERS WITH FLUIDS FROM CULTURES MAINTAINED IN MEDIUM 199 WITHOUT SUPPLEMENTS

—			No. of colds in volunteers receiving			
			Test fluid	Control fluids		
Strain	Passage	Temperature (°C)	Inoculated human cultures	Uninoculated human cultures	Inoculated calf cultures	Inoculated tubes without cells
P.K.	1	33 & 36*	4/9	..	..	0/8
P.K.	1	33	3/7	..	..	..
P.K.	1	36	1/6	..	..	..
P.K.	2	33	2/10	..	..	..
P.K.	2	33	3/14	0/14	..	0/8
P.K.	4	33	0/7	0/5	..	..
H.G.P.	1	33 & 36*	2/9	..	..	0/8
H.G.P.	2	33	1/8	0/5	0/7	..
H.G.P.	2	33	5/16	0/8	0/8	..
H.G.P.	4	33	1/16	0/7	..	..

* A mixture of fluids from cultures maintained at each temperature.

Results with Modified Technique

The experiments were planned to determine as clearly as possible the significance of the colds in volunteers receiving human embryo kidney culture material. They might have appeared because the inoculum enhanced non-specifically a hypothetical latent cold virus infection in the volunteers. This possibility was controlled by giving volunteers uninoculated culture medium containing bovine plasma-albumin at the time at which other volunteers received the test material.

We also tested the possibility that there might be a cold virus latent in the tissue cultures; volunteers were given fluids from a parallel series of passages made exactly as in the test series except that it was started with uninfected broth saline. The third possibility was that the volunteers might be infected by virus carried over from the original washing; to test this we gave fluids from passage series made in culture tubes without cells or in cultures of calf kidney cells; we thought it unlikely that cold virus would grow in calf kidney cells, yet these might nevertheless preserve the virus. At first these control materials were given separately, but in later experiments they were pooled.

The results obtained have been summarised in table II. They show that no colds developed in 78 volunteers who received control material of various sorts, whereas 22 colds developed in 102 who received fluids from cultures inoculated with cold washings. The differences observed for second-passage fluids, when the most strictly controlled trials were made, are statistically significant (P between 0·05 and 0·01). Taken at their face value these results suggest that both the P.K. and H.G.P. cold viruses were transmitted in culture for two passages. Virus probably disappeared by the fourth passages, unless we postulate that it multiplied in a form avirulent for man.

Attempts were made to repeat these experiments using different materials. Human embryo lung cultures were inoculated with P.K. virus, and human thyroid cultures were inoculated with the H.G.P. strain. The D.C. strain of cold used previously (Andrewes et al. 1953) was inoculated into human embryo kidney cultures. No colds were produced when first- or second-passage fluids from these experiments were given to groups of about 8 volunteers (22 volunteers in all); nor did any colds result when two groups of 10 volunteers received second-pass material from human kidney cultures inoculated with each of two "wild" cold washings which had failed to produce colds when administered to volunteers.

Variations in Technique of Passage in Human Embryo Kidney Cells

We attempted to improve the method of cultivation by repeating these experiments systematically, varying the conditions and testing pooled or individual culture fluids in volunteers. The results were not statistically significant but seemed to indicate that transmission probably occurred better at 33°C than 36°C, on harvesting at 4 rather than 2 or 6 days, and on transferring either medium or cell extracts.

In-vitro experiments (Hitchcock and Tyrrell 1960) suggested that the virus might more readily be transmitted when 0·2% of B.P.A., and an extra 0·1% of glucose were added to the maintenance medium. We therefore made

serial passages in culture maintained in this medium starting with second-pass fluids of strains of H.G.P. and P.K. which had produced colds in volunteers. The third strain, F.E.B., was passed at first in medium 199 supplemented with glucose and then with B.P.A. also. In all cases the cultures were maintained at 33° in a roller drum, and passages were made at 5 days using the fluid phase only.

Table III shows that volunteers inoculated with material from the third, fourth, and eighth tissue-culture passages developed colds; they were, however, infrequent in volunteers receiving H.G.P. and P.K. material. Altogether 14 of 71 volunteers who received virus material

TABLE III—COLDS PRODUCED BY INOCULATION OF VOLUNTEERS WITH FLUIDS FROM HUMAN EMBRYO KIDNEY CULTURES MAINTAINED AT 33°C IN MEDIUM 199 SUPPLEMENTED WITH BOVINE PLASMA ALBUMIN AND/OR GLUCOSE

Strain	No. of serial passages	No. of colds in volunteers receiving		
		Test material	Control material	Saline
H.G.P. ..	4	2/16	1/12	..
	8	2/15	1/10	0/5
P.K. ..	8	1/10	1/11	..
F.E.B. ..	3	3/6	0/7	..
	4	2/8	..*	..
	8	4/16	0/6	0/4

*5 volunteers, one of whom developed a cold, have been excluded because the inoculum given was found to be contaminated with Echo 11 virus.

developed colds, while 3 of 55 who received control material did so. This difference is statistically significant ($P < .05$) and strongly suggests that something was being transmitted which could cause colds in man. This conclusion is however mainly due to the results obtained with strain F.E.B. material, and it is possible that the other two strains became attenuated on passage. The significance of our findings is discussed at the end of the third paper in this series (Tyrrell and Parsons 1960).

Summary

We have studied nasal washings from adults with common colds. The causative virus in 5 of 6 washings was not inactivated by ether treatment. One strain (H.G.P.) was tested further and found to be inactivated by human γ-globulin and by treatment at pH 2.

Certain virus strains apparently survived 1 passage in organ cultures of human embryo trachea; others survived 2 but not 4 passages in roller-tube cultures of human embryo kidney maintained at 33° in medium 199. When, however, this medium was supplemented with 0·2% bovine plasma-albumin and an additional 0·1% glucose, colds were produced in significant numbers by third, fourth, and eighth passage material.

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SOME VIRUS ISOLATIONS FROM COMMON COLDS

II. VIRUS INTERFERENCE IN TISSUE CULTURES

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THE first paper in this series (Tyrrell et al. 1960) described experiments in which it appeared that something capable of producing colds in volunteers was being transmitted in tissue cultures of human embryo kidney cells. Clearly it would be of great value to be able to recognise an infected tissue culture without recourse to inoculation of volunteers. We accordingly tested in many ways cultures of the second passage of the H.G.P. and P.K. strains in human embryo kidney cultures. It was not possible to stain cells specifically using the fluorescent-antibody technique. No cytological abnormalities were found in cells stained by usual techniques nor when they were stained for nucleic acids with acridine orange. No excessive loss of cell proteins into the medium was detected. It appeared, however, that when cultures supposedly infected with one of these viruses were inoculated with a second virus, less of the second virus was produced than in control cultures. This finding was used to develop the improved methods of cultivation mentioned in the latter part of the preceding paper.

Methods

Cultures

Human embryo kidney cultures prepared as described by Tyrrell et al. (1960) were used throughout, unless otherwise stated. Medium 199 was used for maintenance and cultures were incubated at 33°C with rolling.

"*Cold viruses*" were those described previously.

Challenge Viruses

The Sendai strain of parainfluenza virus type 1 (Andrewes et al. 1959) was used as infected allantoic fluid. The usual inoculum was about 0·2 hæmagglutinating (H.A.) unit per culture.

The U strain of Echo 11 virus (Philipson and Rosen 1959) was used as a pool of tissue-culture fluid. The usual inoculum was about 0·2 H.A. units or 1000 $I.D._{50}$ per culture.

Hæmagglutination was usually measured using 1% human red cells in phosphate-buffered saline at room temperature.

Demonstration of Interference

Groups of 5–10 tissue cultures were inoculated with virus or control material. 5 days later all or half the medium was removed and challenge virus was added in fresh medium. Incubation was continued for 2 or 3 days and on one or both of these days the hæmagglutinin titre of the medium of each culture was determined. The geometric means of these titres were calculated for each group. A difference of 2 on $\log_2$ scale was regarded as significant on the basis of the statistical analysis of

TABLE I—EXAMPLE OF AN INTERFERENCE EFFECT IN CULTURES CHALLENGED WITH ECHO 11 VIRUS 5 DAYS AFTER RECEIVING COMMON COLD WASHINGS

Inoculum	H.A. titres of individual tubes	$\log_2$ geometric mean H.A. titre	Interference index (by difference)
Washings of patient with cold 2 days after onset	6, 2, 2, 2, 0, 0, 4, 2, 0, 2	0·95 (a)	2·6 (c−a)
Washings of same patient without cold	12, 6, 8, 12, 8, 8, 8, 6, 4, 2	2·7 (b)	0·85 (c−b)
0·5% bovine plasma-albumin in Hanks' saline	8, 8, 16, 6, 32, 16, 16, 16, 8, 8	3·55 (c)	..

some representative experiments. About the same mean titres were found in cultures primarily inoculated with saline, with medium from cultures which had not received cold viruses, or with washings from volunteers without colds. Cultures inoculated with material derived from subjects with colds frequently gave a significantly reduced titre, and a typical experiment is shown in table I. The difference between the log of the mean hæmagglutinin titre of a test group of cultures and that of a control group was calculated and called the interference index.

Results

In the first experiments, washings containing H.G.P. virus were added to cultures and medium from these cultures was transferred to further cultures. These cultures were challenged and found to show interference, which was detected on challenge at 4 or 5 days but not at 2 or 8 days. Interference was demonstrated when either Sendai or Echo 11 virus was used for challenge, but the latter gave more reproducible titres and therefore more significant differences in titre. The differences seemed to be of about the same magnitude whichever virus was used. Other hæmagglutinating viruses were tested but seemed less satisfactory. Results were best read 2 or 3 days after adding the challenge virus; later on, the difference between the infected and control cultures was often much less striking.

TABLE II—INTERFERENCE IN CULTURES INOCULATED WITH HUMAN NASAL WASHINGS

Source of washing	Interference index in cultures receiving washing collected	
	During cold	After cold
Subject:		
S.W.	*2·2*	0·4
F.E.B.	*2·8**	−0·3
P.P.	−0·6	−0·1
D.T.	0·2	−0·3
Pooled washings from volunteers receiving:		
H.G.P.	*4·1*	0·6
D.C.	1·2	..

* Para-influenza-1 virus used in this experiment, Echo 11 in all others. Significant values of the interference index are shown in italics.

Washings were taken from adults suffering from colds and again after they had recovered. These were tested for the presence of virus by the interference method and the results are shown in table II. No interference was detected in cultures receiving material obtained from volunteers who had recovered from their colds but interference was evident in cultures inoculated with material from 2 of 4 natural colds and from 1 of 2 groups of volunteers given experimental colds. No interference was apparent in cultures given second or third passage H.G.P. virus grown without bovine plasma-albumin (B.P.A.) and glucose supplements, a finding in agreement with the results of inoculating volunteers (cf. table II of preceding paper). Interference was also observed in cultures inoculated with 2 other pools of washings obtained from different volunteers inoculated with the H.G.P. strain and with 2 other pools from volunteers receiving the P.K. strain.

In an attempt to improve the sensitivity of the method the medium was supplemented with an additional 0·1% glucose and with 0·2% B.P.A. (fraction V) during the period between inoculation of cold material and inoculation of the challenge virus. Preliminary experiments suggested that both of these measures increased the amount of interference; one such experiment is shown in table III.

Using these supplements, attempts were made to propagate serially the factor which was apparently interfering with multiplication of the challenge virus. As starting material we used the two positive specimens referred to in table II (F.E.B. and S.W.) and the two strains previously studied in volunteers (H.G.P. and P.K.). All but S.W. were successfully propagated through 8 serial tissue-culture passages without difficulty, except that 2 attempts had to be made at the second passage of P.K. These experiments are summarised in the figure. Significant interference was observed at almost every passage. It will be recalled that in the previous paper evidence was presented that fluids from the third, fourth, and eighth passages of F.E.B. caused colds in volunteers.

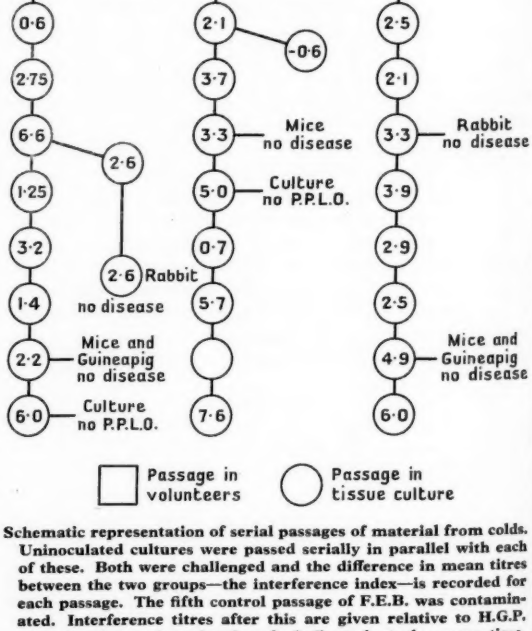
TABLE III—EFFECT OF ADDITIONS TO MEDIUM 199 IN THE DEVELOPMENT OF INTERFERENCE IN CULTURES INOCULATED WITH FLUIDS FROM CULTURES INOCULATED WITH WASHINGS CONTAINING H.G.P. VIRUS

Final concentration (%) in medium of		Interference index*
Glucose	Bovine plasma-albumin	
0·1	0	−0·5
0·1	0·2	2·75
0·2	0	1·25

* Challenged with Echo 11 virus.

Considerable effort was expended in attempts to detect known viruses. It was thought that viruses occurring as contaminants would turn up as readily in the control series as in the series initiated from nasal washings; yet there seems in each passage experiment a regular difference in response between each pair of the two series of cultures.

No hæmagglutinin was detected though culture fluids were tested with human, chicken, ox, mouse, and guineapig cells at



Schematic representation of serial passages of material from colds. Uninoculated cultures were passed serially in parallel with each of these. Both were challenged and the difference in mean titres between the two groups—the interference index—is recorded for each passage. The fifth control passage of F.E.B. was contaminated. Interference titres after this are given relative to H.G.P. control cultures inoculated and challenged at the same time. The numbers in the square representing a passage in volunteers give the proportion of volunteers developing colds.

4°, room temperature, and 37°C, and the cell sheets were tested by hæmadsorption. The fluids were inoculated subcutaneously, intraperitoneally, and intravenously into rabbits without obvious ill effect. Similarly, guineapigs, weanling mice, and 1-day-old suckling mice were inoculated by various routes and all remained well. It was not found possible to cultivate pleuropneumonia-like organisms or other ærobic or anærobic bacteria from the tissue-culture fluids. No interference was detected in cultures of calf kidney, human thyroid, or rhesus kidney cells inoculated with material which produced interference in cultures of human embryo kidney.

Properties of the Interfering Agent

The preceding experiments seemed to indicate that a self-propagating factor had caused the interference and that it had probably originated in the washings. We therefore attempted to find out whether its properties resembled those of the virus which caused colds in volunteers. Experiments on this subject are summarised in table IV. Attempts were made to demonstrate neutralisation by

TABLE IV—SOME PROPERTIES OF THE AGENT WHICH CAUSED INTERFERENCE IN THE SERIES OF EXPERIMENTS INITIATED WITH H.G.P. MATERIAL

Source material	Treatment	Interference index of	
		Treated material	Untreated material
Nasal washing ..	20% ether overnight	5·5	5·5
Second pass T.C. ..	„ „ „	5·25	4·1
Sixth pass T.C. ..	Heat at 56°C for 30 min.	1·3	2·2
Fourth pass T.C. ..	„ „ „ „ „ „	−1·2	2·6
Fourth pass T.C. ..	Passage through gradocol membrane APD 290 mμ.	2·7	2·6
Second pass T.C. ..	Dialysis against citrate buffer pH 2·1 for 3 hr.	−0·8	6·6

pooled human γ-globulin. Apart from one possibly positive result these failed for technical reasons, arising from the toxicity for culture cells of the globulin used. It could nevertheless be concluded that the interfering factor was ether-stable, filtrable, and destroyed by heat (56°C for 30 minutes), and exposure to pH 2. In these respects at least it was apparently identical with the virus producing colds. The effect of acidity and the fact that it was self-propagating distinguished it from interferon (Lindenmann, Burke, and Isaacs 1957).

These results are discussed at the end of the third paper (Tyrrell and Parsons 1960).

Summary

Virus interference has been detected in cultures inoculated with common-cold material and not in cultures inoculated with control material. This interference was found in cultures up to eight in series, maintained in medium 199 modified by increase in the content of glucose and addition of bovine-plasma albumin.

In experiments with H.G.P. material it was found that interference did not develop when the inoculum had been heated at 56°C, or held at pH 2. It did develop when the inoculum had been treated with ether or filtered through a gradocol membrane of average pore-size 290 mμ.

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SOME VIRUS ISOLATIONS FROM COMMON COLDS

III. CYTOPATHIC EFFECTS IN TISSUE CULTURES

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WHEN trying to make the sixth tissue-culture passage of strain P.K., described in the previous paper (Hitchcock and Tyrrell 1960) we found that a new batch of medium 199 was toxic to the cultures. Several different batches of this medium were therefore obtained. These were found to be non-toxic and so an attempt was made to make another passage. In cultures maintained with one of the new batches of medium 199 a definite cytopathic effect was observed after inoculation with tissue-culture fluids thought to contain P.K. and H.G.P. viruses. A preliminary study of this unexpected observation has now been made.

All the materials and methods were as described in the previous papers with the modifications to be found below.

Results

It was thought that the cytopathic effect might have occurred because the new medium 199 contained less bicarbonate (0·09%) than those used previously (0·16%). This was confirmed when it was found that other media with a low bicarbonate concentration allowed the appearance of a cytopathic effect. The development of this effect has been observed in kidney cell cultures, mainly of rhesus monkey but also of human and cynomolgus monkey tissue maintained in a variety of media and inoculated with from one to many thousand infectious doses of virus. We give here a general description of these degenerative changes, which seem to be basically the same under all the conditions studied.

2–7 days after inoculation foci of degeneration are seen. They consist of a few cells in which the cytoplasm becomes refractile or looks like ground-glass. The cells draw away from the surrounding cells and the cytoplasm becomes irregular in outline with long branching processes and small nodules on the cell surface. Later the cells become rounded and fall off the glass. In some cases the foci remain almost unchanged for over a week. In others they gradually extend. In human kidney cultures the foci appear throughout the sheet and extend

TABLE I—CYTOPATHIC EFFECT OF H.G.P. VIRUS IN VARIOUS TYPES OF CULTURES OF KIDNEY CELLS

Species	Variations in the conditions of culture*	Average score of degeneration†	
		At 5 days	At 10 days
Rhesus	Standard	1·2	2·5
	Primary cultures	1	1
	Primary cultures 0·1% bicarbonate	0	0
Rhesus	Standard	2·5	3
	Stationary	1·1	1·5
Rhesus	Standard	2	3
	36°C	0·5	0
Rhesus	Medium 199, 0·16% bicarbonate 36° Primary cultures	0	0
Cynomolgus	Standard	0·8	1·2
Human	Primary cultures	0·8	N.D.

*The standard conditions were the use of secondary cultures maintained at 33°C in a roller drum with a medium containing 2% calf serum and 0·25% lactalbumin hydrolysate in Hanks' saline containing 0·03% sodium bicarbonate. Deviations from these standard conditions are shown but all other conditions remained standard throughout the experiment.

†An arbitrary scoring system was used in which 0·5 represents the appearance of the first few foci of degeneration and 3 represents degeneration of all cells. Groups of 3 to 5 cultures were used.

centrifugally. In rhesus kidney cultures, the foci appear at the extreme edge of the cultures and extend first all round the edge of the cell sheet and then gradually spread in towards the middle. When progressive degeneration of the sheet occurs it only becomes complete 5–10 days after the first focus has been observed. The changes thus resemble those of a very slowly progressive cytopathic effect produced by a poliovirus. Typical cytopathic changes as seen in unfixed and in fixed material are shown in figs. 1–3.

Table I summarises the results of some typical experiments in which the effect of H.G.P. material from the fifth pass in human embryo kidney cultures was studied in various types of cultures maintained in various media. The inoculum was equivalent to 100 tissue-culture infectious doses under standard conditions of culture. The extent of the cytopathic effect was increased by using secondary rather than primary monkey kidney cultures, and by waiting up to 10 days, by using 0·03% bicarbonate rather than 0·1%, 33°C rather than 36°C, and in rolled rather than stationary cultures. Varying the lactalbumin hydrolysate concentration between 0·25% and 1% and the serum concentration between 0 and 4% did not prevent the cytopathic effect but there was at times some inhibition at the higher concentrations. If no bicarbonate was added, cultures became very granular and there was no cytopathic effect due to virus.

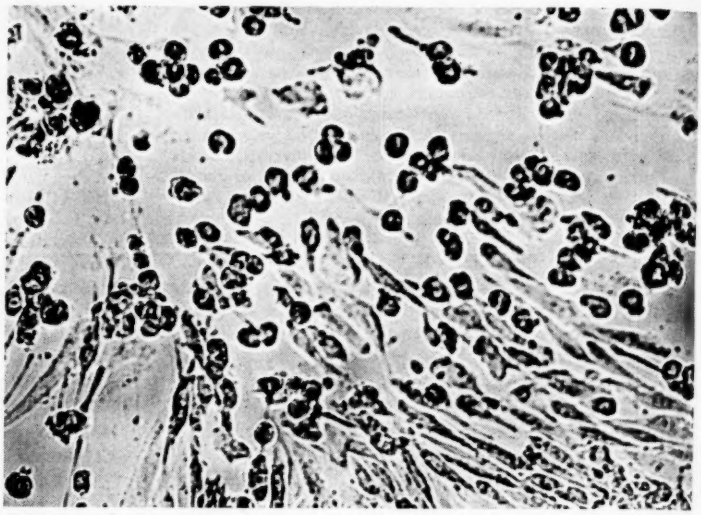

Fig. 2—Similar to fig. 1 but unstained. (× 175).

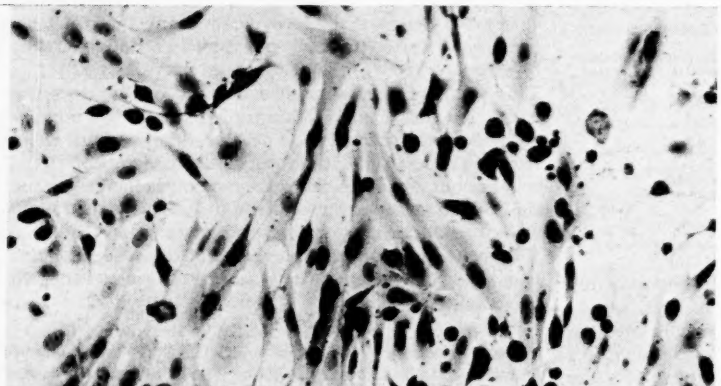

Fig. 1—Secondary cultures of rhesus-monkey kidney cells maintained at 33°C in 2% calf serum, 0·25% lactalbumin hydrolysate with 0·03% bicarbonate and inoculated 8 days previously with 200 T.C.D.$_{50}$ of H.G.P. virus passed 5 times in human embryo kidney cultures. Some spindle shaped cells can be seen but many are rounded up and degenerate. (Hæmatoxylin and eosin. × 175.)

We have formed the opinion that the exact way in which secondary monkey kidney cultures are set up and treated affects the development of cytopathic effect. We now inoculate tubes with 0·5 ml. of growth medium (Tyrrell et al. 1960) containing about 30,000 cells obtained from bottle cultures. The cultures are changed and inoculated about 2 days later when they each contain about 20,000 cells. The cells are in patches rather than continuous sheets at this stage and the pH of the medium is about 7. The cell-count rises to about 30,000 per tube and the pH falls to about 6·5 in the controls by the end of an experiment. Where there is a marked cytopachic effect the pH may be 7 or higher. In other experiments it was found that there was a slight and transitory cytopathic effect in cultures of human

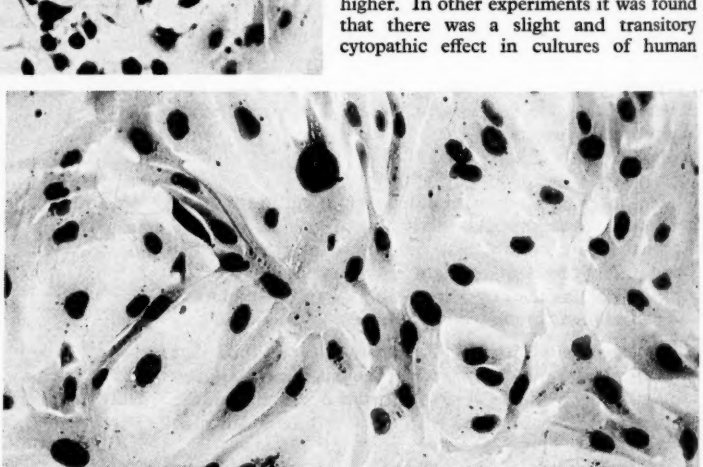

Fig. 3—A parallel culture to that of fig. 1 but not inoculated with virus. No degeneration. (H. & E. × 175.)

TABLE II—THE RELATION BETWEEN THE CYTOPATHIC EFFECT PRODUCED BY H.G.P. VIRUS AND THE INTERFERENCE EFFECT IN HUMAN EMBRYO KIDNEY CELLS

Type of culture *	State of cultures		
	Before challenge	After challenge †	
		Appearance	$\log_2$ Mean HA titre of challenge virus
Human kidney + H.G.P.	Partly degenerate	Partly or completely degenerate	1·9
" " + control inoculum	No degeneration	Complete degeneration	6·4
Rhesus kidney + H.G.P.	Partly degenerate	Complete degeneration	4·0
" " + control inoculum	No degeneration	Complete degeneration	2·1

* All maintained in medium containing 2% calf serum, 0·25% lactalbumin hydrolysate, and 0·03% sodium bicarbonate.
† On fifth day after inoculation with H.G.P. the cultures were challenged with Echo 11.

embryo lung maintained at 33°C in 2% calf serum, 0·25% lactalbumin hydrolysate with 0·03% bicarbonate in the saline. There was no effect in cultures of human thyroid or calf kidney cells maintained under these conditions.

The cytopathic effect has been seen in over 300 cultures of human and rhesus monkey kidney cells inoculated with first to eighth passage material from strains H.G.P. and P.K. With the F.E.B. strain, however, cytopathic effect was seen in human embryo kidney cultures but not after inoculation into monkey kidney cultures. Cytopathic effect was seen in 18 of 19 human or rhesus kidney cultures inoculated with the washings containing H.G.P. and P.K. which were used to initiate the serial cultures mentioned earlier. No effect was seen when the washings were inoculated into cynomolgus kidney cultures. The agent causing this effect has been readily passed in series. The effect has never been seen in over 100 cultures receiving control material, either fluids from cultures of the uninoculated passage series or washings from several volunteers without colds.

This cytopathic effect was compared with the interference effect observed previously. As table II shows, human embryo kidney cultures which showed a cytopathic effect were resistant to reinfection with Echo 11 virus while corresponding rhesus kidney cultures were not. This was in line with previous findings.

Dr. M. S. Pereira of the Virus Reference Laboratory, Colindale, and Dr. D. Hobson of the Virus Research Laboratory, Lodgemoor Hospital, Sheffield, kindly allow us to state that in "blindfold" experiments they have detected cytopathic effects in cultures inoculated with H.G.P. and P.K. strains and none in cultures inoculated with control material.

Properties of the Cytopathic Agents

The cytopathic effect was not prevented by treating the inoculum with ether but it was destroyed by heating at 56°C for 30 minutes and by treatment at pH 2. The cytopathic agent also passed a gradocol membrane of APD 100 mμ. The H.G.P. agent was not destroyed by blending culture medium for 2 minutes at room temperature with 4 volumes of fluorocarbon (Arcton 63) and centrifuging lightly. These experiments were done quantitatively (table III). The infectivity titrations were carried out as with other cytopathic viruses: serial dilutions of virus were inoculated into groups of cultures and the final reading was taken 10–14 days after inoculation. Preliminary attempts were made to identify the H.G.P. virus by neutralisation tests using tissue cultures of rhesus or human kidney cells. 100 TCD_{50} were held at 37°C for 4 hours with serum before inoculation. Cultures were observed for the appearance of specific degeneration. The virus was not neutralised by antisera neutralising Echo 28 (the J.H. and 2060 viruses) and the Coe virus, both of which produce a similar degeneration, have similar physical properties, and are associated with minor respiratory infections (Andrewes 1959). It was not neutralised by hyperimmune typing sera against poliovirus types 1–3, Coxsackie B viruses types 1–5,* nor by pooled sera against Echo viruses types 1–3 and 5–14.†

Neutralisation tests were performed with sera which had been collected from subject H.G.P. at the onset and after the cold during which the washing yielding the H.G.P. strain was taken: the first serum had a titre of less than 5 and the second of 20.

TABLE III—PROPERTIES OF POOLS OF VIRUSES H.G.P. AND P.K. PROPAGATED IN TISSUE CULTURE

Treatment	Titre (T.C.D.$_{50}$ per ml.) of pool of	
	H.G.P.	P.K.
Overnight with 20% ether	$10^{2\cdot3}$	$10>^{4\cdot0}$
Heated 56°C 30 min.	0	0
Exposure to pH 2·1 buffer	0	0
Untreated control	10^{3}	$10>^{4\cdot0}$
Blending with Arcton 63 2 min. and centrifugation	$10^{3\cdot5}$	N.D.
Untreated control	$10^{3\cdot2}$	N.D.
Filtration through collodion membrane of APD 290 mμ	$10^{1\cdot5}$	$10^{2\cdot5}$
100 mμ	$10^{1\cdot3}$	$10^{2\cdot5}$
69 mμ	0	0
Not filtered	N.D.	$10^{2\cdot5}$

0 = titre of less than $10^{0\cdot5}$ per ml. N.D. = not done.

TABLE IV—SUMMARY OF RESULTS OF EXPERIMENTS WITH THE H.G.P. AGENT

—	Result of experiments detecting agent by			
	Colds in volunteers	Interference	Cytopathic effect	
Conditions of culture	*Transmitted*	*Transmitted and/or demonstrated*	*Transmitted*	*Demonstrated*
Medium 199	2 passages	2 passages	2 passages	−*
Medium 199 + BPA and glucose	8 ,, (?)	8 ,,	8 ,,	−
Human embryo kidney 33°C	+	+	+	+*
36°C	−	−	N.D.	−
Human embryo lung 33°C	−	−	N.D.	−
Human thyroid 33°C	−	−	N.D.	−
Rhesus kidney 33°C	−	−	+	+*
Properties of agent				
Heat at 56°C for 30 min.	N.D.	Destroyed	Destroyed	
Ether treatment	Stable	Stable	Stable	
Treatment at pH 2	Destroyed (?)	Destroyed	Destroyed	
Filtration membrane 290 mμ	N.D.	Filtered	Filtered	

* Positive when low bicarbonate medium was used. N.D. = Not done.

Discussion

The finding that some viruses from common colds will grow and produce cytopathic effects in cultures has been reached by following a series of clues. First, as recorded in the first paper of this series, was the evidence of sur-

* Supplied by Dr. P. J. Wormald and prepared by the Central Public Health Laboratory, Colindale.
† Prepared by Microbiological Associates, Washington, D.C.

vival and probable limited growth of a pathogenic agent in tissue cultures of human embryo kidney; tentative conclusions were reached as to what were the best conditions, particularly in regard to the advantages of cultivation at 33°C. Next, the discovery of some interference with growth of other viruses under these conditions of culture permitted experiments less cumbersome than inoculation of volunteers. Thus were discovered modifications of medium leading to more striking results in interference tests and, soon afterwards, to evidence of propagation in series of agents producing colds in volunteers. Finally as an outcome of trouble with 199 medium, it became clear that, in a more acid medium, the virus would produce cytopathic effects in cultures of human embryonic and even rhesus kidney. The summary in table IV shows very good agreement between the results obtained by inoculating volunteers and by looking for interference and for cytopathic effects in cultures. It is, however, worth noting that in rhesus kidney culture, cytopathic effects were seen though interference was not demonstrable. It seems probable that we have cultivated the causative viruses from three cases of the common-cold syndrome. This has been made possible by using human embryonic kidney, and, for some strains, rhesus kidney cultures, and maintaining these at 33°C in an acid medium. These viruses grow poorly if at all under conditions more commonly used for virus cultivation. It is of interest that these cooler and more acid conditions are like those which obtain at the surface of the nasal mucous membrane: we also wonder whether the improved results obtained on adding B.P.A. and glucose to medium 199 were not largely due to lowering the pH of the medium.

The H.G.P., P.K., and F.E.B. viruses under study may, till their significance becomes clearer, be referred to as "Salisbury strains"; whether they are in fact examples of a single kind of virus we do not yet know. Their right to be called common-cold viruses remains to be established. Several myxo- and entero-viruses have lately been recovered from minor respiratory infections, mainly in children, and some of them will produce cold-like symptoms in volunteers. We have, however, not succeeded in isolating any one of them from naturally occurring typical colds of the kind under study at Salisbury (Andrewes 1959). Very possibly these myxo- and entero-viruses are causally related only to atypical "uncommon colds" in adults, the main bulk of common colds having other causes. It will be noted that the Salisbury strains resemble enteroviruses in some respects. The strains now described may or may not prove to be agents responsible for the commonest kind of common cold, the main objective of thirteen years' pursuit at the Salisbury unit. Much further work is needed; they must be sought in washings from colds occurring naturally at different times and places; and better means of studying them serologically must be developed. We anticipate that when further nasal washings are tested, some viruses, resembling H.G.P. and P.K., will be isolated directly using rhesus kidney cells as a host; however, others may be found which, like F.E.B., will produce a cytopathic effect only in human embryo kidney, and others, such as D.C., may fail to grow at all in these hosts.

Summary

A cytopathic effect has been observed in cultures of human and monkey kidney cells inoculated with washings from volunteers with experimental colds and with tissue-culture passage material.

This effect was observed best in cultures maintained at 33°C in a medium containing about 0·03% of sodium bicarbonate.

The agent H.G.P. causing this effect resembled the virus causing colds in volunteers in that it was destroyed by heat and by acid conditions but not by ether treatment. It passed a gradocol membrane of average pore size 100 mμ and was neutralised by convalescent serum from the subject H.G.P.

We wish to thank Dr. J. Field, Dr. A. T. Roden, Dr. J. S. F. Niven, Dr. F. Bang, and Mrs. B. Kelly for help in certain phases of these studies, and also the volunteers whose cooperation made these experiments possible.

Miss J. B. Macdonald, S.R.N., assisted in the volunteer studies. Dr. H. E. M. Kay supplied the human embryo tissue. The monkey kidney tissue and medium 199 were supplied by the laboratory of the Medical Research Council at Hampstead, London. We wish to thank all these for their help and also all our technical staff, particularly Mrs. P. A. Palmer.

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CIRCULATION IN LOWER LIMB BEFORE AND AFTER RECONSTRUCTION OF OBSTRUCTED MAIN ARTERY

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THE treatment of localised obstructions in the main limb arteries by surgical reconstruction has now become standard practice, and provided the reconstructed artery remains patent these patients regain full use of the affected limb (Rob, Eastcott, and Owen 1956).

In a series of patients with severe intermittent claudication due to a localised obstruction in a main artery of the lower limb, we have studied the arterial circulation before and after operative treatment. Such functional studies are few, and are important for a fuller understanding of the circulation in health and disease.

Material and Methods

The 11 male and 1 female patients all had severe unilateral intermittent claudication, and arteriography had shown a short complete block in the iliac, femoral, or popliteal artery. None had clinical evidence of ischæmic disease in the other leg, the brain, or the heart. The clinical details are summarised in table I. The operative details have been described by Eastcott (1953).

Exercise tolerance was determined by walking the patient over two steps, and counting the number of circuits completed before the onset of pain (Hamilton and Wilson 1952).

Blood-flow was measured by water-filled plethysmographs with a venous collecting pressure of 65 mm. Hg. A cuff to occlude the arterial circulation of the foot was placed distal to the calf plethysmograph whose temperature was held at 33° ± 0·5°C, and the limbs were studied consecutively. Reactive hyperæmia was induced by inflating the collecting cuff to 250 mm. Hg for exactly 5 minutes; at the end of this time the blood-flow was recorded by releasing this cuff to 65 mm. Hg, and the measurements were repeated at 30-second intervals

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TABLE I—CLINICAL SUMMARY OF THE 12 PATIENTS

Case no.	Age (yr.)	Sex	Location of block	Duration of symptoms	Preoperative claudication distance	Operation	Postoperative exercise tolerance	Remarks
1	47	M	Short left popliteal	2 weeks	100 yd.	4 cm. frozen homograft	Unlimited	Atheroma
2	42	M	Short lt popliteal	6 mos.	80 yd.	Frozen homograft	,,	Thrombosed fusiform aneurysm
3	50	M	Right femoropopliteal junction ..	6 mos.	6 min. walking	9 cm. homograft	Unlimited (up to 20 miles)	..
4	25	M	Short rt popliteal	2 mos.	100 yd.	Freeze-dried homograft	Unlimited	Cystic medial necrosis with thrombosis
5	48	M	1·5 cm. calcified occlusion of rt common iliac	10 yr. Some weeks	$^1/_2$ mile A few yards	Thrombo-endarterectomy	,,	Calcified atheroma
6	50	M	4 cm. lt popliteal with nearby atheroma	3 mos.	Less than $^1/_4$ mile	Frozen homograft	Slight limitation, no claudication	..
7	50	M	Short rt superficial femoral	Several months	300 yd.	5 cm. frozen homograft	Unlimited	..
8	46	M	Rt popliteal	5 yr.	30 yd.	11 cm. frozen homograft	,,	Thrombosed saccular aneurysm
9	52	M	Lt common iliac	5 yr.	300 yd.	Thrombo-endarterectomy	,,	..
10	53	M	Lt popliteal	5 mos.	5 min. walking	Frozen homograft	,,	..
11	61	M	Middle third of lt femoral	1 mo.	20 yd.	Autogenous 12 cm. vein graft	,,	..
12	44	F	Short lt popliteal	2 yr.	100 yd.	6 cm. frozen homograft	,,	..

thereafter for 5 minutes by reinflating the cuff to this pressure. Blood-flow was measured simultaneously in both feet with plethysmograph temperatures ranging from 30 to 45°C, but not varying by more than ± 1°C in any one experiment. The subject was heated by immersing one or both arms in a stirred-water bath at 44–45°C; for cooling, water baths of 17–18°C were used, and, in some patients, ice was applied to the chest,

TABLE II—EXERCISE TOLERANCE BEFORE AND AFTER OPERATION

Case no.	Days	Before operation circuits	Days	After operation circuits
1	1–2	18–19	35	58–60
3	1–7	11–14	22	40
4	1	15	150	53
5	6	12–13	5	45
6	2–3	12–14	120	55
7	4	17–18	21	25
8	7	12	56	64
9	21	7	35–63	30–43
10	1–56	9–19	102–150	23–34
11	1–21	19–23	28	34–56

and the room temperature lowered; with this exception, room temperature was maintained at 23–24°C. All blood-flow rates are expressed as ml. per 100 ml. of tissue per minute, and each is a mean of at least four consecutive measurements at intervals of 30 seconds, except during reactive hyperæmia where individual rates of flow are recorded.

Results

Exercise Tolerance

Table II shows the number of circuits over the steps which the patient completed before the onset of claudication pain; where more than one test was performed, the range is shown. After operation, claudication could not be provoked by the test in any patient except cases 6, 9, and 10, whose exercise tolerance was, however, considerably improved and in whom arteriography showed a patent main arterial channel. These results agree with the symptomatic improvement reported in a similar, but much larger, series (Rob et al. 1956) and with the experience of many other workers. Further occlusion of limb arteries developed subsequently in some patients; this conforms with the well-recognised natural history of atheroma. After 400 reconstructive operations on arteries, followed for eighteen months or longer, Rob (1960) reports further arterial thromboses in 87.

Calf Blood-flow

Before operation, the resting blood-flow through each calf was about the same, but the pattern of reactive hyperæmia in the two limbs was very different. In the symptomless limb the flow was maximal at the moment of release of the circulation, and declined rapidly in the following $1^1/_2$ minutes. This is the normal response described by Lewis and Grant (1925). In the affected limb there was no detectable flow on release, and the maximal flow did not develop until $1^1/_2$ minutes later. Fig. 1 compares the flows (mean and 95% confidence limits) of the affected and symptomless legs of 8 patients before operation, and shows the abnormal pattern, and

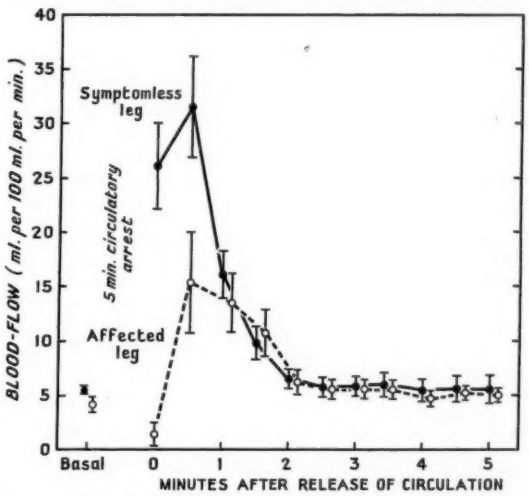

Fig. 1—Calf blood-flows at rest and during reactive hyperæmia of the patients' affected and symptomless limbs before operation: mean and 95% confidence limits.

TABLE III—BLOOD-FLOW THROUGH THE CALF (ML. PER 100 ML. TISSUE PER MIN.) BEFORE 5 MIN. ARREST OF THE CIRCULATION AND AT $^1/_2$ MIN. INTERVALS THEREAFTER

Group	Mean age	No. of limbs	Mean resting flow	Release flow	Minutes after release of circulation								
					$^1/_2$	1	$1^1/_2$	2	$2^1/_2$	3	$3^1/_2$	4	$4^1/_2$	5
Old normal	64	9	6·6 ±0·48	38·1 ±4·16	36·4 ±4·39	20·7 ±4·08	13·9 ±1·77	8·9 ±0·96	8·4 ±0·60	8·0 ±0·68	7·6 ±0·70	7·4 ±0·77	7·4 ±0·69	7·3 ±0·66
Young normal	28·3	9	5·5 ±0·73	38·2 ±7·8	35·5 ±6·31	20·3 ±2·33	11·4 ±1·60	8·5 ±1·32	7·7 ±1·26	7·0 ±0·86	7·0 ±0·93	7·2 ±0·97	7·0 ±1·17	6·3 ±0·93
Patients' symptomless limb	50·6	8	5·5 ±0·86	26·0 ±4·85	31·5 ±4·73	15·9 ±2·26	9·8 ±1·54	6·5 ±0·93	5·7 ±0·92	5·8 ±0·92	5·9 ±1·17	5·4 ±0·98	5·5 ±1·24	5·5 ±1·31
Patients' affected limb:														
Before operation		8	4·15 ±0·70	1·2 ±1·0	15·3 ±4·87	13·3 ±2·67	10·7 ±2·18	6·3 ±1·31	5·5 ±0·91	5·45 ±0·89	5·5 ±0·84	4·7 ±0·77	5·2 ±0·60	4·9 ±0·60
After operation		8	7·6 ±1·27	20·8 ±4·51	25·2 ±2·84	18·3 ±2·04	12·6 ±1·12	8·8 ±0·81	8·6 ±0·98	8·3 ±0·91	7·9 ±0·70	8·0 ±0·95	8·1 ±0·84	8·4 ±0·97

low values, of the hyperæmia flows in the diseased limbs. Shepherd (1950) showed a similar slow development of maximal blood-flow in limbs with arterial insufficiency both after exercise and after circulatory arrest.

For comparison with our patients, we made control studies of the calf reactive hyperæmia in 12 men who had

Fig. 2—Calf blood-flows at rest and during reactive hyperæmia of healthy or normal subjects and the patients' limbs after operation: mean and 95% confidence limits.

neither symptoms nor signs of vascular disease; 6 of these were aged 20–35 and 6 were aged 55–75. Table III compares the blood-flow (mean and standard error) at rest and at half-minute intervals during reactive hyperæmia in the controls and patients before and after operation. The two age-groups of the controls show very similar values, and the results have therefore been pooled for comparison with the patients in fig. 2. This shows that the resting flow increases after operation, becoming greater than that in the control group, and that the hyperæmia pattern returns to normal. However, the flows attained in the operated leg during the initial part of the hyperæmia are lower than those in the symptomless limbs, and these in turn are lower than in the normal limbs. These relationships may reflect the integrity of the respective arterial trees, the symptomless limb being affected by clinically inapparent arterial disease, and the affected limb after operation having an arterial circulation inferior to that of its fellow, owing either to a greater amount of arterial disease or to inability of the graft to furnish a completely normal lumen. The return of normal reactive hyperæmia in our patients following operation suggests that the abnormal pattern was due to the localised obstruction in the main artery, and not to disease of smaller vessels or other factors. Eastcott (1953) and Gaskell (1956) found the same abnormal hyperæmia curve in patients with arterial obstruction; the pattern returned to normal when the obstruction was relieved surgically, but it reverted if the artery was occluded by further thrombosis (Gaskell 1956).

Reactive hyperæmia may be regarded as the "repayment" of a blood-flow "debt" incurred during the period of circulatory arrest. The volume of the blood debt has been estimated by assuming that the mean basal blood-flow before arrest of the circulation would have continued unchanged during the next 10 minutes if there had been no interference. Thus the blood debt is this rate of flow multiplied by 5 (the minutes of circulatory arrest), and the repayment is the area of the reactive hyperæmia curve lying above this assumed basal flow. Mean values of debt and repayment and an analysis of their relationship are shown in table IV. The mean percentage repayment for each group has been calculated from individual repayments expressed as a percentage of their respective debts.

TABLE IV—GROUP MEANS AND STANDARD ERRORS OF THE 5-MINUTE BLOOD-FLOW DEBT, REPAYMENT, AND REPAYMENT AS PERCENTAGE OF DEBT WITH THE SIGNIFICANCE OF ITS DIFFERENCE FROM 100; AND COEFFICIENT OF CORRELATION BETWEEN DEBT AND REPAYMENT WITH ITS SIGNIFICANCE

Group	No. of limbs	Debt	Repayment	% repayment of debt	Difference from 100% of percentage repayment		Correlation between debt and repayment	
					t	P	r	P
Control	18	30·3 ±2·3	38·0 ±3·8	133·7±13·9	2·43	<0·05>0·02	+0·25	>0·1
Patient's symptomless limb	8	27·4 ±4·3	25·5 ±4·1	103·0±19·7	0·17	>0·1	+0·33	>0·1
Patients' affected limb:								
Before operation	8	23·1 ±3·5	16·5 ±4·2	74·4±17·6	1·45	>0·1	+0·08	>0·1
After operation	8	38·2 ±6·4	23·1 ±3·5	77·0±18·7	1·23	>0·1	−0·57	>0·1

The smaller repayments and percentage repayments of the patients' affected and symptomless limbs is a further expression of the lower hyperæmia curves of these groups, already noted in fig. 2. Operation produced a surprisingly small increase in percentage repayment (from 74 to 77), apparently at variance with the good clinical response. The explanation of this paradox may lie in the failure of the method to distinguish between skin and muscle blood-flow. It has already been observed that the resting calf flow is increased after operation (fig. 2), and it is shown later that operation is followed by up to an eightfold increase in blood-flow through the foot. This suggests that operation induces vasodilatation in the limb, mainly in the skin; and hence the blood-flow debt, calculated from the resting calf flow, is larger than that due to muscle alone. Since reactive hyperæmia is mainly due to increased blood-flow through muscle, the true percentage repayment of calf muscle after operation is probably much greater than that calculated.

If hyperæmia were regulated exactly to redress the debt, the mean percentage repayment should not differ significantly from 100. Table IV shows that the percentage repayment of the control group (133·7) differed significantly from 100 ($t = 2{\cdot}43$, $0{\cdot}02 < P < 0{\cdot}05$), but it did not do so in the remaining groups. For each group a correlation coefficient of debt and repayment has been calculated, and their values and significance are shown in table IV. There was no consistent relationship between them. Freeman (1935) suggested that reactive hyperæmia was a homœostatic mechanism with the blood debt accumulated during ischæmia nicely balanced by the hyperæmia. Our results offer no support for this theory, but suggest that the magnitude of reactive hyperæmia is mainly related to the efficiency of the arterial circulation.

Apart from the general errors of plethysmography there are some special sources of error that must be borne in mind in considering these results. It is known that the arterial blood-pressure beyond an arterial obstruction may be lower than elsewhere (Edholm et al. 1951), and furthermore Patterson and Whelan (1955) have shown that, on release of the circulation after a period of arrest, the arterial blood-pressure in the normal arm may take 20 seconds or more to return to its previous level. It is therefore possible that, in some of the affected limbs studied before operation, the collecting-cuff pressure of 65 mm. Hg may have obstructed the entry of blood into the limb and caused falsely low estimates of flow. To investigate this possibility some of the experiments were repeated with a lower pressure in the collecting cuff; the values were found to be the same or slightly higher, and the same abnormal pattern remained in the reactive hyperæmia curve.

Foot Blood-flow

Blood-flow through the foot was measured serially in 7 patients before and after operation (table V). As would be expected, the symptomless limb usually had the greater rate of flow, especially at the higher plethysmograph temperature, but there were exceptions (cases 2–4); the special circumstances of case 5 will be described later. Without exception, operation was followed by a temporary, and often large, increase in blood-flow through the foot of the affected limb, often exceeding that in the contralateral foot. This response to operation, which will henceforth be termed the postoperative vasodilatation, was maximal 1–5 days after operation, and declined during the next few days. The degree of postoperative vasodilatation was not related to the preoperative circulatory efficiency (judged by the exercise-tolerance test and calf and foot flows) or to any other obvious factor. It was present throughout the range of plethysmograph temperatures used, and was therefore not a response to local heat. Most of these cases had a repair of an obstructed popliteal artery, so it remains uncertain whether the site of obstruction and repair is a

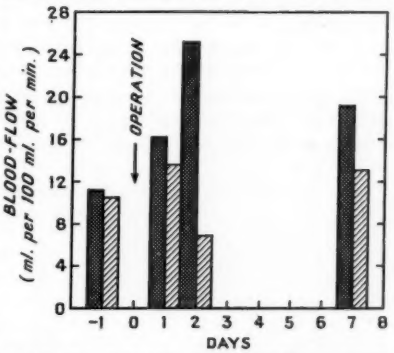

Fig. 3—Case 2: foot blood-flows (plethysmograph temperature 43°C) before and after popliteal grafting. Stippled columns = operated limb. Hatched columns = symptomless limb.

TABLE V—MEAN BLOOD-FLOWS THROUGH FEET IN ML. PER 100 ML. PER MINUTE BEFORE AND AFTER REPAIR OF OCCLUDED MAIN ARTERIES

Case no.	Site of arterial obstruction	Plethysmograph temperature (°C)	Foot	Days before and after operation													
				−5 or before	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10 or after
1	Lt popliteal	43	L	4·6	..	..	..	..	..	..	33·3	..	39·7	..	..	..	22·5	14·8
			R	16·5							8·0		11·9				16·6	10·5
2	Lt popliteal	43	L	..	..	..	..	11·0	16·1	25·1	..	..	..	..	18·8	..	..	..
			R	..	..	..	..	10·3	13·4	6·8	..	..	..	..	13·3	..	..	..
		32	L	..	..	..	..	..	..	..	13·8	..	3·6	..	..	..	..	..
			R	..	..	..	..	..	..	..	3·7	..	1·1	..	..	..	..	..
3	Rt popliteal	40	R	9·8	..	..	..	..	13·0	..	7·0	..	14·2	..	..	10·4	..	11·0
			L	19·2	..	..	..	..	12·0	..	7·4	..	7·6	..	..	18·5	..	9·4
		30	R	..	..	..	4·1	..	..	3·2	5·4	..	..	3·4	..	2·6	..	..
			L	..	..	..	4·1	..	..	0·8	2·0	..	..	1·6	..	2·8	..	..
4	Rt popliteal	33	R	3·6	..	3·3	5·8	4·2	21·0	11·0	..	..	5·3	..	..	6·7	..	..
			L	3·6	..	3·6	5·4	4·0	4·2	2·2	..	..	3·8	..	..	2·1	..	..
5	Rt iliac. Previous rt sympathectomy; aorta and lt iliac dissected. Rt iliac thromboendarterectomy	31	R	9·6	..	..	10·0	8·7	..	..	12·0	..	..	..	..	11·5	..	..
			L	3·6	..	..	2·0	1·1	..	..	16·4	..	..	..	..	1·4	..	..
		44	R	..	8·4	..	..	6·9	..	..	11·5	..	..	..	..	..	16·0	..
			L	..	14·5	..	..	15·5	..	..	19·7	..	..	..	..	..	17·3	..
6	Lt popliteal	44	L	..	..	8·3	..	..	18·1	..	..	15·6	..	..	..	..	..	9·9
			R	..	..	19·4	..	..	12·5	..	..	12·1	..	..	..	..	..	17·5
7	Rt femoral	44	R	..	..	..	..	5·1	..	..	7·1	..	..	..	..	..	..	9·4
			L	..	..	..	..	10·7	..	..	8·1	..	..	..	..	..	..	8·3

factor of importance in producing this phenomenon. Gaskell (1956) has shown that the same phenomenon sometimes appears after repair of occluded iliac and femoral arteries, and our clinical experience agrees with this.

Fig. 3 shows the postoperative vasodilatation in case 2. On the 2nd postoperative day the foot blood-flow in the operated side was more than double the preoperative flow in either foot, and on the other side was less than at any other time. Cases 1 and 6 showed the same reduction of blood-flow in the symptomless limb during the peak of postoperative vasodilatation.

ROLE OF VASOMOTOR TONE IN POSTOPERATIVE HYPERÆMIA

To define the role of the sympathetic nerves in limbs with postoperative vasodilatation we studied the effect of heating the body. This completely removes sympathetic

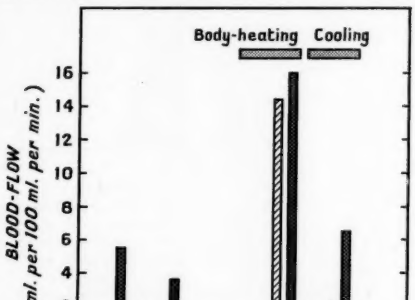

Fig. 4—Case 2: effect of body heating and cooling on foot blood-flows 5 days after operation. Plethysmograph temperature 32°C. Stippled columns = operated limb. Hatched columns = symptomless limb.

vasoconstriction in the hand, but less completely in the foot (Pickering and Hess 1933). When applied to patients with postoperative vasodilatation, body-heating produced a rise in the blood-flow till approximately the same high level was attained in both feet (fig. 4, case 2). When the body was cooled, blood-flow fell on both sides, but less on the operated side. Similar results were found in further 2 patients and the response to body heating of all 3 patients is shown in table VI. It will be seen that the notable difference in blood-flows through the two feet was largely abolished by heating the body.

These experiments demonstrate that the sympathetic nerves are still capable of altering vascular tone in the foot during the phase of postoperative vasodilatation, and that when sympathetic tone is released the vascular beds in the two feet are of similar size. Hyperæmia due to a chemical vasodilator stimulus or to an enlarged vascular bed would both be expected to maintain a greater blood-flow in the affected limb even upon release of sympathetic tone. Our observations on the postoperative vasodilatation are fully consistent with its being due to partial release of sympathetic constrictor tone.

NATURE OF OPERATIVE STIMULUS PRODUCING VASODILATATION

Table V shows that in case 5 profound postoperative hyperæmia developed in the unaffected limb; thus the features of this case are of special interest.

TABLE VI—MEAN BLOOD-FLOWS THROUGH THE AFFECTED (A) AND SYMPTOMLESS (S) FEET AFTER POPLITEAL ARTERIAL GRAFTING: FLOWS IN ML. PER 100 ML. PER MIN. BEFORE AND AFTER HEATING THE BODY

Case no.	Days after operation	Plethysmograph temperature (°C)	Foot	Before heating	After heating
2	5	32	A	3·6	15·9
			S	1·1	14·5
	7	43	A	18·8	28·9
			S	13·3	28·9
3	2	30	A	3·2	3·4
			S	0·8	3·0
4	1	33	A	21·0	29·4
			S	4·2	23·8
	5	33	A	5·3	20·7
			S	3·9	17·0

This patient had a block about $^3/_4$ in. long in the right common iliac artery, and 6 weeks before our studies a right lumbar sympathectomy had been performed elsewhere. We confirmed that the right foot remained devoid of vasomotor innervation by observing that the blood-flow through this foot did not change with vigorous body heating and cooling. At operation the aortic bifurcation and both common iliac arteries were mobilised by dissecting off the densely adherent periarterial tissues. Controlling clamps were placed on the aorta and both common iliac arteries, and then the calcareous mass obstructing the right common iliac artery was extracted from it. The incision in the artery was then closed.

Fig. 5 shows the foot blood-flow in this patient before and after operation, using plethysmograph temperatures of 44 and 31°C. Before operation the affected side had the greater flow when the plethysmograph temperature was 31°C (owing to the previous sympathectomy), but this side had the lesser flow when the plethysmograph was 44°C (owing to the obstruction in its main artery). On the 1st postoperative day both pulses had returned in the right foot, but it was the left foot that was red and hot, being appreciably warmer than the right. This difference in temperature persisted until the 7th postoperative day when once again the right foot was warmer than the left, as had been the case before operation. Blood-flow measure-

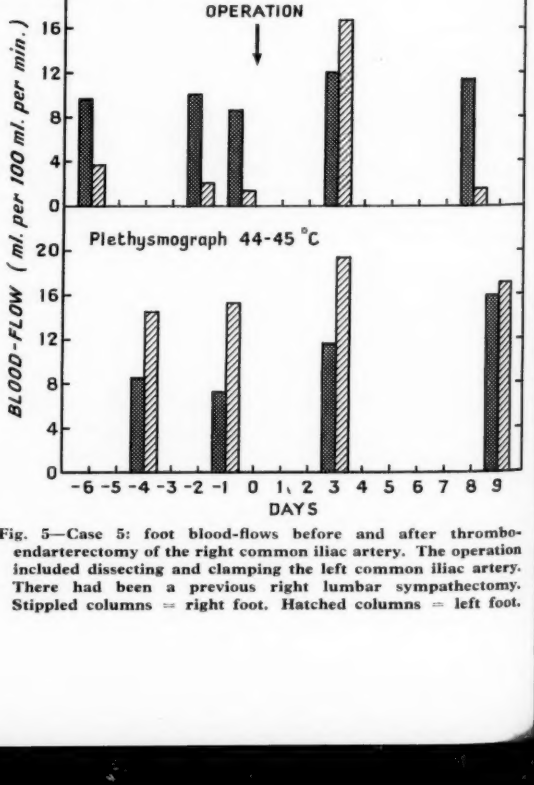

Fig. 5—Case 5: foot blood-flows before and after thromboendarterectomy of the right common iliac artery. The operation included dissecting and clamping the left common iliac artery. There had been a previous right lumbar sympathectomy. Stippled columns = right foot. Hatched columns = left foot.

ments (fig. 5) confirmed that the left (unaffected) limb had experienced an appreciable postoperative vasodilatation which had subsided by the 8th postoperative day, whilst there was no evidence of vasodilatation of this kind on the affected side. The vasodilatation must have been related to the operative interference upon the aorta and left common iliac artery, for this patient had no more than the usual rise of body temperature of 1–2°F after operation. The vasodilatation in the left foot was similar in kind, degree, and duration to that seen in other cases on the grafted side, and suggests a similar mechanism. On the 8th postoperative day the blood-flow through the left foot increased in response to body-heating from 1·3 to 8·8 ml. per 100 ml. per min., demonstrating that the operation had not destroyed the sympathetic nerves supplying the left leg.

The only factor common to the interference with this normal limb and the reconstructive operations of other patients was the handling and dissection of the main artery. This suggests the possibility that postoperative vasodilatation is due to injury of the artery or destruction of the periarterial plexus of nerves. The latter mechanism seems more likely in view of the other evidence suggesting that the response was mediated by a partial release of sympathetic vasomotor tone.

Discussion

Striking changes followed reconstruction of the main artery in these patients. One or both of the foot pulses returned during the operation or shortly afterwards, and the foot became hot and red, often for several days. The blood-flow through the resting calf as well as through the foot was greater in the operated than in the contralateral limb for many days after operation.

Calf Blood-flow

Intermittent claudication was largely, or completely, relieved by operation and the reactive hyperæmia returned towards the normal pattern. The reversal of these abnormalities after operation suggests that in the main they resulted from a single obstruction in a main artery.

The slight impairment of reactive-hyperæmia flows in the calves of both operated and symptomless limbs is probably due to further, lesser, arterial obstructions; such measurements are of value in the study of groups of patients, but the overlap with the normal deprives them of individual diagnostic significance.

The response of blood-flow to ischæmia was termed reactive hyperæmia by Lewis and Grant (1925), who considered that it was occasioned by the accumulation of metabolites. Further, in 1938 Grant showed that the hyperæmia following exercise was governed by the amount of exercise undertaken, and that it was independent of the sympathetic nerves. Freeman (1935) claimed that a self-regulating system must be responsible for the approximate correlation which he demonstrated between the blood debt incurred during circulatory arrest and the subsequent excess flow. It has been found that the excess blood-flow of reactive hyperæmia and after exercise is independent of the resting flow whether this has been elevated by heating the body (Barcroft et al. 1952) or reduced by infusing adrenaline (Dornhorst and Whelan 1953). Similarly the excess flow is no greater when the effective local blood-pressure is reduced, or when arterial hypoxia is induced (Dornhorst and Whelan 1953). It was therefore postulated by Barcroft and his colleagues (1952) that two functionally independent types of vessels existed in muscle: one responding to metabolites and the other under the control of the sympathetic nerves. Dornhorst and Whelan (1953), however, considered that these findings were adequately explained by assuming that the removal or destruction of metabolites depended on a concentration gradient from tissues to the vessels, and not on the level of blood-flow or oxygen tension. Patterson and Whelan (1955) found, like us, a poor correlation between blood debt and repayment, and a percentage repayment ranging from 50 to 200. Duff et al. (1955) observed the effect of antihistamine drugs on reactive hyperæmia and found evidence for the accumulation of histamine only when the circulation had been arrested for 10 minutes or longer. There is evidence that the transmural pressure of arteries may partly govern their calibre (Bayliss 1902), Folkow 1949, Greenfield and Patterson 1954), and that this mechanism may play a part in reactive hyperæmia (Patterson 1956).

Thus many factors may be responsible for reactive hyperæmia, and in these circumstances it is perhaps not surprising that there should be only an approximate relation between blood-flow debt and repayment. In our subjects the repayment reflected the integrity of the arterial circulation, being greatest in the normal group, intermediate in the patient's symptomless leg, and least in their affected leg. Furthermore those patients with the greatest circulatory impairment had the smallest repayments.

We infer from these results that, in the healthy subject, the excess blood-flow during reactive hyperæmia is not regulated exactly to balance the debt incurred by ischæmia. By the action of multiple factors this hyperæmia may be normally well in excess of homœostatic requirements and its extent largely a reflection of the integrity of the arteries.

Foot Blood-flow

The major point of interest resulting from the studies on foot blood-flow is its temporary, and often large, increase following repair of the main artery; a similar temporary increase in foot blood-flow following arterial grafting was reported by Eastcott (1953) and by Gaskell (1956), who concluded that restoration of the arterial pathway—and not any other aspect of the operation—was the cause of the hyperæmia. There is much evidence from our own and other studies that the arterial vessels of an ischæmic limb may be dilated, and it might be supposed that the increased flow after operation is simply due to a higher pressure within persistently dilated vessels. However, as both our and Gaskell's studies show, in the ischæmic limb the vessels are more dilated in muscle than in skin, whereas the postoperative increase of flow is much more prominent in skin than in muscle. In addition we have produced a similar hyperæmia in a normal limb where the only interference was dissection of the periarterial tissues. Although we cannot yet identify with certainty the cause of the postoperative vasodilatation, our data suggest the tentative hypothesis that the phenomenon is due to a partial release of sympathetic vasomotor tone, caused by the destruction of the periarterial nervous plexus at operation.

The effect of destroying the periarterial sympathetic nerves on the blood-flow in the limb has long been disputed, and physiological aspects have been lost sight of amid the conflicting therapeutic claims.

Perivascular denervation was first suggested by Jaboulay (1899) and was later strongly advocated as a treatment for ischæmic disease by Leriche (1921). Leriche found that denuding the artery of its sheath over a length of 8 to 10 cm. caused contraction of the artery, with loss of its pulse, and a fall of the skin temperature of the operated limb lasting 3–15 hours. The pulse then reappeared and the limb became noticeably warmer, its temperature exceeding that of the unoperated side by 2–3°C. This vasodilatation was transitory, however, waning 5-6 days later, and vanishing within 3–4 weeks. Brown and Rowntree (1925) measured the heat elimination

from the hand in a patient with Raynaud's disease before and after periarterial sympathectomy. After operation, the elimination increased to a maximum in 5–8 days and returned to its pre-operative level in 2 weeks. In a patient with Buerger's disease, these workers found no changes in heat elimination from the hand after periarterial sympathectomy. Rogers and Hemingway (1930) studied the problem in cats. The change of the hindlimb volume to histamine and acetylcholine injections was measured before and after destruction of the periarterial nerves. Soon after operation, vasodilatation could be shown by this method, though evidence of it had disappeared by the end of the experiment. They obtained more direct evidence of vasodilatation by observing the vessels of the rabbit's ear; after destruction of the periarterial nerves of the carotid artery, the ear remained redder and warmer than the other side for 48 hours. Woollard and Phillips (1932) measured the skin temperature of their own hands before and after injecting procaine around the radial and ulnar arteries. With this method they were unable to detect any changes, but there was no reliable evidence of paralysis of the periarterial nerves. Other published work on periarterial sympathectomy deals solely with the clinical appraisal of its sequelæ. However, the time relationships of the clinical improvement in the circulation and its subsequent relapse followed, in many cases, the pattern described by Leriche.

The postoperative hyperæmia exhibited by our patients is therefore similar in degree and duration to the changes recorded by previous workers after division of the periarterial nerves. We therefore consider that division of periarterial nerves is the likeliest main cause of the postoperative vasodilatation here described.

Summary

In 12 patients with a localised obstruction of the iliac, femoral, or popliteal artery, the arterial circulation was investigated by plethysmography before and after reconstructive operations. The obstruction was relieved by an arterial homograft in 9, by an autogenous vein graft in 1, and by thromboendarterectomy in 2.

After operation intermittent claudication was greatly relieved or abolished.

Blood-flow through the calf was measured at rest, and during reactive hyperæmia, in 8 patients and in a control group of 12 healthy men. In the affected limb, resting calf flow was sometimes equal to, or even greater than, that in the contralateral limb, but the calf reactive-hyperæmia curve had an abnormal form, and was lower than in the other limb. The normal calf reactive hyperæmia was greater than that in the patients' symptomless limbs. In the early postoperative period, the affected limb had the larger resting flow, and its reactive-hyperæmia curve became higher and assumed a normal shape.

The percentage " repayment " by reactive hyperæmia of a calf blood-flow " debt " incurred by 5 minutes' circulatory arrest averaged 134 in the normal group, 103 in the patients' symptomless limb, and 74 in the affected limb. These findings suggest that reactive hyperæmia is not a nicely balanced response, but a vasodilatation induced by many independent causes with the integrity of the arteries as a limiting factor.

Foot blood-flow was measured serially in 7 patients. Preoperatively it was usually, but not invariably, reduced on the affected side. After operation the foot flow in the operated limb increased in all patients, in 5 of them exceeding the flow in the other foot for several days. Evidence is adduced that this postoperative vasodilatation is due to partial release of sympathetic tone induced by interruption of the periarterial plexus of nerves.

These studies were suggested by Sir George Pickering, to whom we are grateful for encouragement. Our thanks are also due to Prof. C. G. Rob for allowing us to study his patients.

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TECHNIQUE OF IRRADIATION OF CONSCIOUS PATIENTS UNDER INCREASED OXYGEN PRESSURE

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IT has been known for many years that plant cells are more susceptible to damage when irradiated under aerobic than under anaerobic conditions, and in experiments with the roots of *Vicia faba* Thoday and Read (1947) showed that, as the oxygen tension rises from zero, the radiosensitivity also increases—steeply at first but more slowly later. In 1953 Gray et al. established that in mice the sensitivity of the Ehrlich ascites tumour is raised by high oxygen tension. Clinically, Churchill-Davidson et al. (1955, 1957) demonstrated the enhanced effect of radiation on patients breathing oxygen at 3 atmospheres pressure, and reported some promising results with the method.

This treatment under oxygen at high pressure involved the use of a metal pressure chamber, general anæsthesia to enable patients to tolerate the chamber, and bilateral myringotomy to prevent damage to the middle ears. As ill patients could not have repeated anæsthesia, two large treatments only were given; and, because of the time taken to anæsthetise and prepare the patients, only a few could be treated. The normal method of irradiation by fractionation daily for a number of weeks could not be applied, and the treatment could not be used as a routine for large numbers of patients. A further disadvantage was that the anæsthesia might well decrease the sensitivity of the tumour cells, thus partially counteracting the beneficial effects of the high-pressure oxygen (Burdick 1953).

In an attempt to obviate these disadvantages, we decided to investigate the possibility of treating large numbers of conscious patients under high oxygen tension with the usual fractionation techniques. For this purpose we

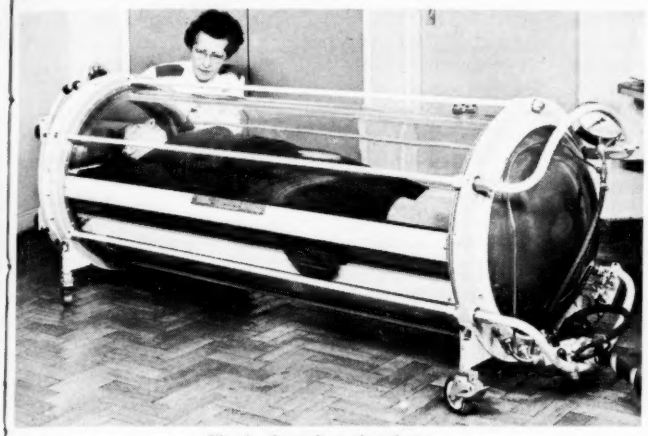

Fig. 1—Complete chamber.

needed a pressure chamber which would be acceptable to the average conscious patient, and would be applicable to routine radiotherapy techniques, without shortening the time in which the machines were in use. The special problems posed by these requirements were:

1. Production of a mobile chamber, able to withstand at least 1 atmosphere above ambient, which would allow continuous visual and auditory contact with the patient.
2. Elimination of any features which would make the conscious patient unwilling to undergo this form of treatment.
3. Elimination of the risk of an explosive decompression, which might endanger bystanders and affect the patient because of the sudden drop in pressure.
4. Development of a system of pressurisation which would at least minimise ear and sinus pain or damage (otitic sinus barotrauma). These syndromes are caused by difference of pressure between the environment and the sinus and middle-ear cavities.
5. Provision of adequate ventilation, to give full oxygenation and to prevent retention of water vapour and carbon dioxide inside the chamber.

The Chamber

A transparent chamber, pressurised through an electromechanical automatic control system, was designed and constructed (fig. 1). It is a ' Perspex ' cylinder (6 feet long and 26 inches in internal diameter) mounted on wheels. Its ends are fibre-glass domes supported in aluminium rings. One end dome is removable and is used for entrance of the patient, who lies on a movable bed (fig. 2). In an emergency the chamber can be depressurised from 1 atmosphere above ambient within half a minute. To remove the risk of an explosive decompression the perspex cylinder is made as a double skin whose interlayer is partially filled with glycerin. This distributes the stresses between the two parts of the structure, and, in the remote possibility of the inner skin failing, the pressure would be retained by the outer skin.

All the control gear is mounted on a small panel remote from the chamber and connected to it by a flexible hose 100 feet long. The flow of oxygen from cylinders to the chamber can be varied; in practice a flow of approximately 5 cubic feet per minute has been found satisfactory. This gives good pressurisation, rapidly sweeps residual air out of the chamber (which has a volume of about 20 c. ft.), provides a comfortable environment for the patient, and prevents the build-up of water vapour and carbon dioxide. The pressure inside the chamber is controlled by a motorised spring-loaded valve on the outlet side. This valve, when set, gives a constant rate of pressure change; this setting can be varied from 1 to 2 lb. per sq. in. per minute by adjusting the speed of rotation of the motor. The layout of the control system, is shown in fig. 3. An intercommunication system is incorporated in the apparatus so that the patient, the operator of the chamber, and the radiographer giving the treatment, can be in constant communication with each other.

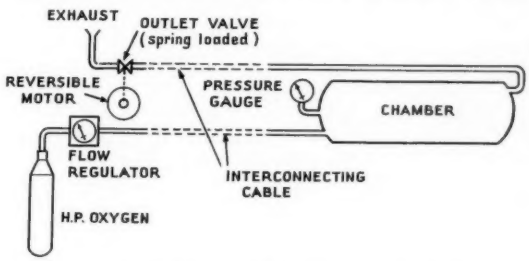

Fig. 3—Layout of the chamber pressurisation system.

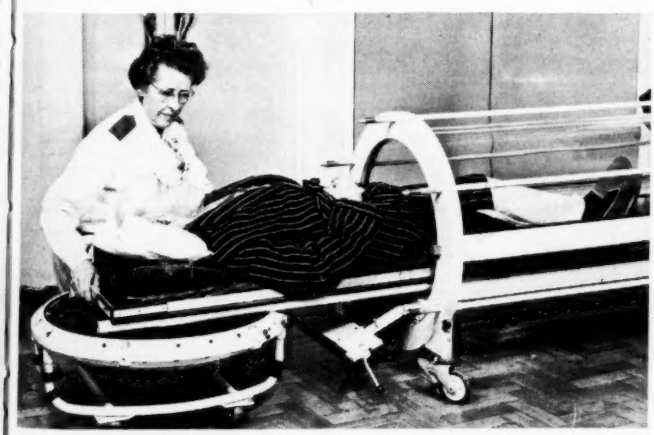

Fig. 2—Method of entry of the patient.

Experience of the Method

This chamber has been employed since January, 1959, for the treatment of patients with carcinoma of the bronchus by the techniques in use in the radiotherapy department at University College Hospital (Hilton and Pilcher 1955). These entail daily treatment for from four to seven weeks. The patients have withstood their radiotherapy well and the transparency and ease of communication have enabled them to enter the chamber with confidence. As in normal techniques, the irradiation is applied under visual control and the patient can be observed throughout. The mobility and small size of the chamber make possible its use with the standard radiotherapy units. The total time from entering the chamber to the end of depressurisation is usually under half an hour, and, as pressur-

isation and depressurisation take place outside the treatment room, the radiotherapy machine can be in continuous use. The whole technique is simple and has not necessitated any increase in staff. It should be noted that although the rate of pressure change used is normally 2 lb. per sq. in. per minute, there has been no pain or damage in ear or sinus. This may possibly be attributed to the smooth pressurisation attained by the automatic control system.

In view of the success of this chamber, we hope to develop the technique so that it can be used for treating conscious patients at pressures up to 4 atmospheres absolute.

We are grateful to Dr. Gwen Hilton, director of the radiotherapy department, University College Hospital, and to Dr. C. F. Bareford, managing director, Vickers Research Ltd., for their invaluable help and encouragement in this project.

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INVESTIGATION OF HYPERPARATHYROIDISM IN THE ABSENCE OF BONE DISEASE

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MANY patients with hyperparathyroidism present with renal calculi and not with the classical features of bone disease, hyperphosphatasia, hypercalcæmia, hypophosphatæmia, and hypercalciuria; in some of them disturbances of serum-calcium or plasma-phosphorus are absent.

Because of the known effect of parathyroid hormone on the renal tubules (see, for example, Hiatt and Thompson 1957) many investigators have studied the renal handling of phosphate in hyperparathyroidism. Phosphate-clearance (Kyle, Schaaf, and Canary 1958), and the ratio of phosphate-clearance to creatinine-clearance (C_P/C_{Cr}) (McGeown 1957), have been investigated extensively; a phosphate-excretion index (P.E.I.) (Nordin and Fraser 1956) and percentage tubular reabsorption of phosphate (%T.R.P.) (Goldman, Gordan, and Chambers 1957, Thomas, Connor, and Morgan 1958) have been derived from the clearance ratio. But none of these indices of phosphate disturbance have given an unequivocal distinction between patients with hyperparathyroidism and those with renal calculi associated with other conditions.

We have used a technique described by Anderson (1955a) to study the theoretical renal phosphorus threshold in proven cases of hyperparathyroidism, and in other patients with no evidence of parathyroid overactivity. So far a clear distinction has emerged between patients with hyperparathyroidism and those with idiopathic renal calculi.

Patients Studied

GROUP 1. *Hyperparathyroidism.* (Cases 1–7)

Seven patients had hyperparathyroidism proven by surgical removal and histological examination of adenomata. Six presented with renal calculi and one had malignant hypertension without renal calculi or nephrocalcinosis. None had biochemical or radiological evidence of bone disease.

GROUP 2. *Renal calculi.* (Cases 8–17)

Ten patients with calcareous renal calculi were comparable in age and range of renal function with those of group 1. These patients were not considered to have hyperparathyroidism, and therefore none was explored for parathyroid lesions.

GROUP 3. *Idiopathic hypercalciuria.* (Cases 18–20)

Three patients had idiopathic hypercalciuria. Case 18 had had multiple renal calculi for 9 years. Case 19 had nephrocalcinosis. Case 20 had had recurrent renal calculi for 20 years, and exploration of the neck in October, 1957, revealed normal parathyroid glands.

GROUP 4. *Others.* (Cases 21–28)

Two patients had idiopathic phosphaturia; in one it was associated with renal glycosuria, and in the other with aminoaciduria. Three were normal hospital patients. Two were cases of acromegaly. One was a case of steatorrhœa with osteomalacia.

Methods

Measurement of Renal Phosphorus Threshold

Outline of procedure.—A linear rise in plasma-phosphorus of about 8 mg. per 100 ml. was produced by an intravenous infusion of buffered sodium phosphate over a period of 180 minutes. Urine was collected at 30-minute intervals, and blood was taken at the mid-point of each urine-collection period. The inorganic phosphorus in each blood and urine sample was estimated. (In this paper "plasma-phosphorus" refers to the plasma-inorganic-phosphorus level.) Plasma-phosphorus was then plotted against time to confirm that a linear rise had occurred, and the plasma-phosphorus at the mid-point of each urine-collection period was obtained by interpolation. The theoretical renal phosphorus threshold was calculated from a second graph with the urinary phosphorus excretion (mg. per min.) in each period as ordinate and the corresponding plasma-phosphorus as abscissa. The regression line was calculated. The plasma-phos-

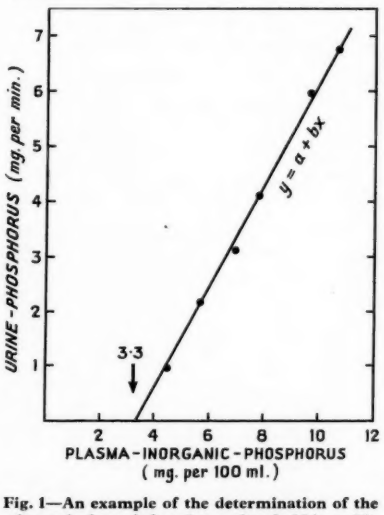

Fig. 1—An example of the determination of the theoretical renal phosphorus threshold (case 15).

The six points represent the plasma-phosphorus levels and urinary output of phosphorus during six periods of infusion. The regression line was calculated ($y = -3{\cdot}2 + 0{\cdot}96x$), and the point at which it cuts the abscissa, defined as the theoretical renal phosphorus threshold, was 3·3 mg. per 100 ml.

TABLE I—FINDINGS IN PATIENTS WITH HYPERPARATHYROIDISM

Case no.	Sex	Age (yr.)	History of calculi (yr.)	Serum-calcium		Plasma-ionised-calcium		Plasma-phosphorus		Urine-calcium (mg. per day)		Creatinine-clearance (ml. per min.)	Blood-urea (mg. per 100 ml.)	Renal phosphorus threshold (mg. per 100 ml.)
				No. of tests	Range (mg. per 100 ml.)	No. of tests	Range (mg. per 100 ml.)	No. of tests	Range (mg. per 100 ml.)	Calcium intake normal	Calcium intake low*			
1	M	30	None	11	9·4–13·3	1	8·2	12	1·8–3·0	254–280	48	84	36	0·9
2	F	31	7	5	13·1–14·3	3	10·0–10·5	5	1·3–2·4	338–544	268	81	25	1·0
3	F	44	>4	10	9·5–12·5	5	6·2–7·3	10	2·0–3·9	464–482	193	80	34	2·0
4	F	48	25	8	9·6–12·3	1	7·2	8	2·9–4·0	248–270	175	73	46	2·0
5	F	55	1	1	14·4	1	9·6	2	2·3–2·4	..	..	73	39	0·8
6	M	61	13	2	9·8–10·5	2	5·4–6·4	3	2·5–2·8	273–293	92	72	46	1·4
7	M	64	4	5	11·0–12·1	2	6·2–6·7	5	2·4–3·0	238–446	130	89	35	1·6
Mean		47·6	..	..	11·96	..	7·65	..	2·5	..	..	79	37·3	..

* Less than 150 mg. calcium per day for 5 days.

phorus corresponding to the point at which the regression line cuts the abscissa is defined as the theoretical renal phosphorus threshold. Results of a typical infusion are shown in fig. 1.

Details of the infusion.—The buffered sodium phosphate (pH 7·4) comprised Na_2HPO_4 52·4 g. and $NaH_2PO_4.2H_2O$ 11·5 g. in 1 litre of sterile distilled water; this contains 1·37 g. of inorganic phosphorus per 100 ml. The infusions were begun at about 10 A.M., with the patient fasted for 12 hours, and resting in bed. A linear rise in plasma-phosphorus was produced by injecting every 60 seconds a calculated volume of phosphate from a sterile graduated 20-ml. syringe through polyethylene tubing into an arm vein. Initially we used the method of Anderson (1955a) for calculating the desired rate of infusion. We have since found it possible to inject an initial volume of 0·7 ml. per min., increasing progressively to 1·6 ml. per min. at 180 minutes in most patients. If there were gross abnormalities in the size of the patient or the glomerular-filtration rate (G.F.R.), the rate of injection was adjusted by calculation. About 200 ml. of the phosphorus solution (90 mM of P, 163 mEq. of Na) was infused. A water diuresis was maintained by the patients' drinking 250 ml. of water every 30 minutes. Urine specimens were obtained at approximately $^1/_2$-hour intervals, timed to the nearest $^1/_2$ minute. Women had an indwelling many-holed catheter inserted, and the bladder was washed out with sterile isotonic saline after each collection period. At the intended midpoint of each urine-collection period 8 ml. of blood was taken from an indwelling needle in a limb not being used for infusion, mixed with 120 units of phosphate-free heparin, and centrifuged immediately.

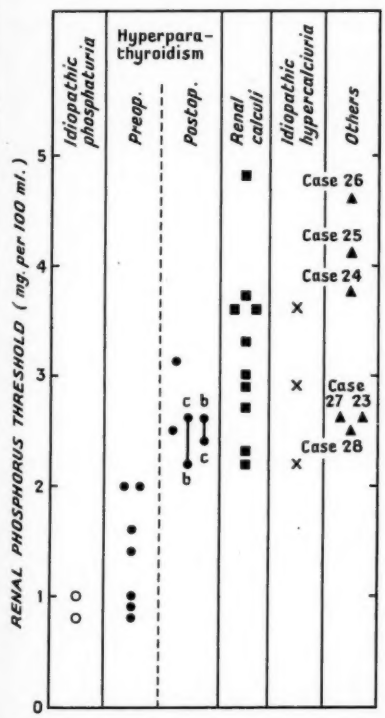

Fig. 2—The theoretical renal phosphorus threshold in the twenty-eight patients investigated.

In the group of determinations after parathyroidectomy, the points coupled by a line represent two determinations in the same patient at (*b*) 11 days and (*c*) 5 months after operation. (See table VI.)

Other Investigations

Just before most of the infusions, blood was taken from the fasting patient for estimation of the serum-calcium, plasma-ionised-calcium, plasma-phosphorus, and plasma-creatinine. The creatinine output during each period of infusion, the pre-infusion fasting C_P/C_{Cr} ratio from 8 A.M. to 10 A.M., and the creatinine-clearance were determined; the P.E.I. was also calculated.

In twenty-one infusions the phosphate reabsorbed by the renal tubule was calculated in successive 30-minute periods; the difference between ph e excreted in the urine (mg. per min.) and in the filte load (G.F.R. × plasma-P) was regarded as the reabsorbed phosphate. During the periods chosen the plasma-phosphorus level was higher than the renal-phosphorus threshold, and the tubular reabsorption of phosphorus was presumably maximal (Tm_P). In five patients the G.F.R. was measured by inulin infusion; in the remainder endogenous creatinine-clearance was used.

Analytical Methods

Calcium: Kramer and Tisdall (1921), and the Eppendorf flame photometer. Ionised calcium: Rose (1957). Phosphorus: Briggs (1922). Creatinine: Peters (1942). Urea: Peters and Van Slyke (1932). Inulin: Roe, Epstein, and Goldstein (1949).

Normal Limits

The following normal ranges have been established for this laboratory:

	Mean ± S.D.	*95% limits*	*80% limits*
Serum-calcium (mg. per 100 ml.):			
Kramer and Tisdall	9·9 ± 0·66	8·6–11·2	9·0–10·8
Flame photometer	9·3 ± 0·53	8·2–10·4	8·6–10·0
Plasma-phosphorus (mg. per 100 ml.)	3·6 ± 0·64	2·3–5·0	2·7–4·4

Plasma-ionised-calcium (mg. per 100 ml.): normal range 5·1–6·9 (16 determinations in eight subjects).

Values outside the 95% limits are regarded as definitely abnormal, while those between the 80% and 95% limits are suspicious; values within the 80% limits are regarded as normal. Serum-calcium levels determined by flame-photometry are marked with a dagger (†) in the tables. Normal values for the C_P/C_{Cr} ratio vary with the plasma-phosphorus level, and we have judged our results by the criteria of McGeown (1957). The normal range of P.E.I. is ±0·12 (Nordin and Fraser 1956); patients with hyperparathyroidism would be expected to give values higher than +0·12. Tm_P in fasting normal subjects on a normal diet is reported by Anderson (1955a) as 4·4–5·5 mg. per min., and by Thompson and Hiatt (1957) as 73–199μM (2·3–6·2 mg.) per min.

Results

The results are summarised in fig. 2.

GROUP 1. *Hyperparathyroidism.* (Cases 1–7; tables I and IV)

a. Before Parathyroidectomy

The renal phosphorus threshold was 2·0 mg. per 100 ml. or less in all seven patients.

In four patients (cases 1, 3, 4, and 6) the serum-calcium was normal at least once during the preoperative period,

TABLE II—FINDINGS IN PATIENTS WITH RENAL CALCULI

Case no.	Sex	Age (yr.)	History of calculi (yr.)	Serum-calcium		Plasma-ionised-calcium		Plasma-phosphorus		Urine-calcium (mg. per day)		Creatinine-clearance (ml. per min.)	Blood-urea (mg. per 100 ml.)	Renal phosphorus threshold (mg. per 100 ml.)
				No. of tests	Range (mg. per 100 ml.)	No. of tests	Range (mg. per 100 ml.)	No. of tests	Range (mg. per 100 ml.)	Calcium intake normal	Calcium intake low *			
8	M	25	>2	1	9·8	2	3·7–3·9	1	3·0	..	..	111	..	2·7
9	M	35	8	1	9·5	1	5·1	1	3·0	..	..	113	..	3·6
10	F	42	>1	3†	8·8–9·6	0	..	3	2·7–3·5	..	..	95	24	4·8
11	M	50	7	1†	9·4	1	5·3	1	2·3	..	..	103	35	2·2
12	M	51	3	4	9·8–10·8	2	5·3–6·2	4	2·4–3·4	92–154	44	67	44	2·9
13	F	59	1	4†	10·0–10·4	1	5·1	4	2·6–3·6	202–254	..	59	36	3·7
14	F	46	1	4	9·3–9·6	2	5·4–5·6	4	3·3–4·7	185–200	..	82	21	3·6
15	M	52	15	1	10·1	1	4·5	1	3·1	..	..	..	23	3·3
16	M	55	16	1	9·5	1	5·8	1	3·3	..	..	..	35	2·3
17	M	55	28	1	9·6	1	5·6	1	3·0	..	..	..	31	3·0
Mean		47	..	..	9·7	..	5·16	..	3·07	..		90	31	..

* Less than 150 mg. calcium per day for 5 days. † By flame photometry.

and on four separate occasions in case 1 when on a normal diet. Case 6 had a consistently normal serum-calcium, but it rose to 11·1–11·3 mg. per 100 ml. after a low-phosphorus diet (610 mg. per day) supplemented with aluminium hydroxide for 10 days.

Whenever they were both measured, the plasma-ionised-calcium was normal when the serum-total-calcium was normal. In particular, in case 6, the plasma-ionised-calcium did not exceed 6·4 mg. per 100 ml. (which is within our normal range, and that of 5·9–6·5 mg. per 100 ml. described by Lloyd and Rose 1958).

On the day of infusion, the fasting plasma-phosphorus at 10 A.M. was not definitely abnormal in six patients. Repeated determinations (not necessarily fasting) gave at least one abnormal reading in three patients (cases 1–3), one patient (case 4) had a consistently normal plasma-phosphorus level, and three patients (cases 5–7) had levels that were never definitely abnormal.

In the six patients studied, the urinary calcium excretion exceeded 250 mg. per day on a normal diet. In three of them the daily urinary calcium excretion fell to less than 150 mg. when the calcium intake was reduced to less than 150 mg. per day for 5 days; we regard this as a normal response (see Hodgkinson and Pyrah 1958). In the other three cases the urinary calcium excretion remained abnormal.

In all cases the creatinine-clearance was within the range 72–89 ml. per min. The response to 5 units of pitressin tannate in oil intramuscularly was normal in one with a maximum urine specific gravity of 1024 (case 3), impaired in three (cases 4, 6, and 7), and not tested in the other three.

The C_P/C_{Cr} ratio and the P.E.I. were normal in case 1 on three occasions, and in case 4 on the only occasion it was measured. Total plasma-proteins, alkaline phosphatase, and potassium were normal in all patients.

b. After Parathyroidectomy (table IV, fig. 2)

The renal phosphorus threshold, redetermined in four patients (cases 2–4 and 6) 10–13 days after parathyroidectomy, was found to be more than 2·0 mg. per 100 ml. in each case. There was no significant change in their creatinine-clearance, but the response to pitressin improved in the three patients in whom it was impaired before parathyroidectomy.

The renal phosphorus threshold, reinvestigated in two patients (cases 2 and 3) 5 months after parathyroidectomy, was more than 2·0 mg. per 100 ml.

GROUP 2. *Renal Calculi.* (Cases 8–17; tables II and IV)

The lowest renal phosphorus threshold found was 2·2 mg. per 100 ml.

The serum-calcium was definitely normal in nine patients and suspicious (10–10·4 mg. per 100 ml. by flame photometry) in one (case 13). Plasma-ionised-calcium was normal in the nine cases in which it was measured, including case 13. The fasting plasma-phosphorus was normal in seven patients, and suspicious (2·3–2·6 mg. per 100 ml.) on one occasion in cases 11–13.

Urinary calcium excretion was normal in the three patients investigated. The range of renal function assessed by creatinine-clearance or blood-urea was similar to that of the patients with hyperparathyroidism. The ratio C_P/C_{Cr} and P.E.I. were normal in five cases (8–11, and 13), abnormally high in case 12, and not measured in cases 14–17.

GROUP 3. *Idiopathic Hypercalciuria.* (Cases 18–20; tables III and IV)

The renal phosphorus threshold was 2·2 mg. per

TABLE III—FINDINGS IN PATIENTS WITH IDIOPATHIC HYPERCALCIURIA AND IN OTHER CONDITIONS

Case no.	Diagnosis	Sex	Age (yr.)	Serum-calcium		Plasma-ionised-calcium		Plasma-phosphorus		Urine-calcium (mg. per day)		Creatinine-clearance (ml. per min.)	Blood-urea (mg. per 100 ml.)	Renal phosphorus threshold (mg. per 100 ml.)
				No. of tests	Range (mg. per 100 ml.)	No. of tests	Range (mg. per 100 ml.)	No. of tests	Range (mg. per 100 ml.)	Calcium intake normal	Calcium intake low*			
18	Idiopathic hypercalciuria	F	39	8	9·4–10·9	1	5·1	8	2·5–3·7	260–445	68	91	29	3·6
19	" "	M	43	4	8·9–10·4	1	5·3	4	2·8–3·9	556–635	340	117	34	2·9
20	" "	M	46	6	9·3–11·2	3	4·6–5·0	6	2·7–3·2	398–460	106	87	37	2·2
21	Idiopathic phosphaturia	F	47	7	9·1–10·3	0	..	7	1·2–2·1	264	..	100	25	0·8
22	" "	F	56	3	10·1–10·4	0	..	3	1·0–2·2	48–110	..	..	22	1·0
23	Normal	M	19	1	10·9	0	..	1	3·2	..	..	151	34	2·6
24	"	F	39	3	9·3–9·6	1	5·4	2	3·4–3·5	..	..	85	23	3·8
25	"	F	60	1	10·2	0	..	2	3·2–3·4	..	..	59	..	4·1
26	Acromegaly	F	27	2†	9·5	0	..	2	4·3–5·2	..	..	125	20	4·6
27	" (inactive) ..	F	62	2	10·4–10·8	1	5·2	2	3·1–3·5	..	..	87	26	2·6
28	Steatorrhœa and osteomalacia	M	61	2	7·4–7·9	0	..	3	1·3–2·6	..	..	98	25	2·5

* Less than 150 mg. calcium per day for 5 days. † By flame photometry.

100 ml. or higher in three patients with "idiopathic hypercalciuria".

In one patient (case 19) hypercalciuria persisted when the dietary intake of calcium was less than 150 mg. for 5 days; in the other two the urinary calcium output fell to less than 150 mg. per day.

Case 20 had on one occasion a serum-calcium level of 11·2 mg. per 100 ml., but it was normal on five other occasions. Case 18 had suspicious serum-calcium levels (10·9 mg. per 100 ml.) on three occasions. Plasma-ionised-calcium, plasma-phosphorus, C_P/C_{Cr} and P.E.I. were never abnormal.

GROUP 4

a. Idiopathic Phosphaturia. (Cases 21–22; tables III and IV)

The renal phosphorus threshold in two cases with a "renal phosphate leak" were among the lowest found in this series (0·8 and 1·0 mg. per 100 ml.). Both had consistently low levels of plasma-phosphorus, high C_P/C_{Cr} ratios, and high P.E.I. The serum-calcium was normal.

b. Miscellaneous. (Cases 23–28; tables III and IV)

Six other patients who had no evidence of hyperparathyroidism all had renal phosphorus thresholds above 2·4 mg. per 100 ml. Although case 28 had severe osteomalacia, bone biopsy showed "Wide osteoid seams are present. There is no increased osteoblastic or osteoclastic activity" (Dr. J. L. Pinniger). This helps to exclude secondary hyperparathyroidism.

One patient with inactive acromegaly and mild pituitary insufficiency (case 27) had an abnormally high C_P/C_{Cr} and P.E.I.

Measurement of Tm_P

In fourteen infusions the reabsorbed phosphate varied greatly in successive periods and the Tm_P could not be defined. These fluctuations were not related to changes in G.F.R., and they occurred when both inulin and creatinine were used as measures of G.F.R. There was no significant change in plasma-creatinine during any infusion. Data from a representative group of patients are shown in table V.

TABLE IV—COMPARISON OF INDICES OF PHOSPHATE METABOLISM ON THE DAY OF INFUSION (ALL AVAILABLE DATA)

Case no.	Renal phosphorus threshold (mg. per 100 ml.)	Plasma-phosphorus (mg. per 100 ml.)	C_P/C_{Cr}	P.E.I.
1 (*a*)	0·9	2·4	0·09	+0·02
2 (*a*)	1·0	2·5	0·30	+0·22
(*b*)	2·1	3·3	0·26	+0·14
(*c*)	2·6	2·9	0·11	+0·01
3 (*a*)	2·0	2·1	0·24	+0·19
(*b*)	2·6	2·9	0·21	+0·11
(*c*)	2·4	2·2	0·11	+0·05
4 (*a*)	2·0	4·2	0·27	+0·11
(*b*)	3·6	3·6	0·24	+0·11
5 (*a*)	0·8	2·5	0·65	+0·56
6 (*a*)	1·4	2·5	..	..
(*b*)	2·5	3·6	..	..
7 (*a*)	1·6	3·0	..	..
8	2·7	3·7	0·23	+0·10
9	3·6	3·0	0·08	−0·02
10	4·8	3·5	0·12	−0·01
11	2·2	2·2	0·09	+0·03
12	2·9	2·4	0·24	+0·17
13	3·7	3·4	0·02	−0·10
18	3·6	3·3	0·07	−0·05
19	2·9	3·5	0·05	−0·08
20	2·2	3·2	0·14	+0·02
21	0·8	1·2	0·42	+0·41
22	1·0	1·8	0·52	+0·48
23	2·6	3·2	0·03	−0·08
25	4·1	3·4	0·08	−0·04
26	4·6	5·2	0·11	−0·10
27	2·6	3·5	0·30	+0·19
28	2·5	2·6	0·10	+0·02

a = preoperative.
b = 10–13 days after parathyroidectomy.
c = 5 months after parathyroidectomy.

TABLE V—G.F.R., TUBULAR REABSORPTION OF PHOSPHATE, AND RENAL PHOSPHORUS THRESHOLD IN SELECTED PATIENTS (SEE TEXT)

Case no.	Range of G.F.R. (ml. per min.)	Phosphate reabsorbed in successive periods during the infusion (mg. per min.)						Renal phosphorus threshold (mg. per 100 ml.)
2 (*a*)	73–82	1·1	1·2	1·6	1·8	2·6		1·0
(*b*)	88–95	2·6	3·0	3·1	3·2			2·1
(*c*)	67–74‡	2·0	2·4	1·9	1·6			2·6
3 (*a*)	75–90	1·4	1·5	1·4	1·6	1·6		2·0
(*b*)	70–76	1·9	2·0	2·0	1·7	1·7	2·2	2·6
(*c*)	69–75	1·7	1·5	1·7	1·9	1·4		2·4
4 (*a*)	68–76	2·3	2·6	2·4	3·3	3·6		2·0
(*b*)	63–75	2·5	2·7	3·5	3·1			3·6
13	52–62	1·8	1·4	1·1	1·1	1·2		3·7
20	83–94‡	2·4	2·1	2·6	2·1			2·2
27	80–93	2·0	1·3	1·4	0·4	0·6		2·5

a = preoperative.
b = 10–13 days after parathyroidectomy.
c = 5 months after parathyroidectomy.
‡ Inulin-clearance.

The extremes of variability are shown in cases 2(*a*) and 27. In most cases showing a consistent trend, tubular reabsorption increased in successive periods, but in four (cases 2[*c*], 10, 13, and 27) it decreased.

In cases 2 and 3 phosphate reabsorption had increased 10–13 days after parathyroidectomy, but in case 4 no significant change was detected, although the renal phosphorus threshold had increased considerably. Moreover, in cases 2 and 3, the Tm_P 5 months after parathyroidectomy was indistinguishable from the preoperative value, while the renal phosphorus threshold had increased to within normal limits, and there was no evidence of active hyperparathyroidism.

Results of Phosphate Infusion

The plasma-phosphorus level 15 minutes from the end of the infusion was 9–15 mg. per 100 ml. The mean rise in plasma-phosphorus achieved in hyperparathyroid patients was 7 mg. per 100 ml., and in patients with renal calculi 8·7 mg. per 100 ml.

A fall in serum-calcium was noted in all infusions in which it was investigated, and it varied from 0·6 to 4·1 mg. per 100 ml., the greatest falls being in patients who had high fasting serum-calcium levels. In one patient with severe osteomalacia (case 28) the fall in serum-calcium from 7·9 mg. to 5·2 mg. per 100 ml. was accompanied by tetany which responded to intravenous calcium gluconate.

None of the patients experienced malaise, rigors, or venous thromboses.

Discussion

Theoretical Renal Phosphorus Threshold

Operation confirmed the diagnosis in all seven patients who had renal phosphorus thresholds of 2·0 mg. per 100 ml. or lower, and who were considered to have hyperparathyroidism.

The renal phosphorus threshold was of particular value in three patients in whom at least two of the classical diagnostic criteria were normal. Case 1 had normal serum-calcium levels on four of eleven occasions, had a normal urinary calcium output when on a low-calcium intake, had a normal C_P/C_{Cr} ratio and P.E.I. on three occasions, and a normal response to two calcium infusions

(Nordin and Fraser 1954). Case 4 had a consistently normal plasma-phosphorus, and a normal C_P/C_{Cr} and P.E.I. Initially case 6 had consistently normal levels of serum-calcium and plasma-ionised-calcium, but lowering the phosphorus intake did eventually elevate the serum-calcium above normal. This patient also had a normal urinary calcium excretion when on a low-calcium intake.

The fact that the renal phosphorus threshold rose to the normal range within 13 days of parathyroidectomy in the four patients tested indicates that it depends on parathyroid function. It seems to be a valuable index for the identification of hyperparathyroidism in patients with renal calculi or nephrocalcinosis.

We must point out that, with the exception of case 20, none of the patients with idiopathic hypercalciuria or idiopathic renal calculi were operated upon, and that there is slender evidence of hyperparathyroidism in some (suspicious levels of serum-calcium in cases 13, 18, and 20, and of plasma-phosphorus in cases 11, 12, and 13) but this diagnosis was considered very unlikely on all the available evidence.

The renal phosphorus threshold is, of course, lowered in certain patients with primary disorders of renal tubular function (e.g., cases 21 and 22), but these patients can usually be separated by the demonstration of defects such as aminoaciduria, glycosuria, or acidosis, and they lack other evidence of hyperparathyroidism.

In the three normal patients (cases 23–25) the renal phosphorus threshold varied between 2·6 and 4·1 mg. per 100 ml. compared with Anderson's (1955a) range of 4·0–4·7 mg. per 100 ml. in six young adult males.

Serum-calcium Levels

All seven patients with hyperparathyroidism had hypercalcæmia at some stage, although in case 6 this was only seen after a low-phosphate intake. In three cases (1, 3, and 4) which were followed for 2–7 years, the hypercalcæmia was intermittent (compare Bogdonoff et al. 1956, McGeown and Morrison 1959). Lloyd and Rose (1958) found increased ionised calcium and normal total calcium in two of seventeen patients with hyperparathyroidism; measurement of ionised calcium is, therefore, potentially a more sensitive index than measurement of total calcium, but in our experience it has not yet proved to be so (see also Loken and Gordan 1959).

Plasma-phosphorus Levels

The plasma-phosphorus levels overlap considerably between all four groups of patients, and, like many investigators (including Goldman et al. (1957) and McGeown and Morrison (1959), we think this is an unreliable index of hyperparathyroidism.

Impaired renal function may result in normal or raised plasma-phosphorus levels in patients with hyperparathyroidism. From the data of Goldman and Bassett (1954), this seems unlikely when the G.F.R. is higher than 50 ml. per min. All our patients with hyperparathyroidism had creatinine-clearances greater than 70 ml. per min., and we consider that the frequent presence of normal plasma-phosphorus levels was not due to renal dysfunction but is a feature of the disease.

Phosphate-clearance

Clearance of phosphate by the kidney shows much diurnal variation, is minimal at 8 A.M., and is related to the plasma-phosphorus level (Stanbury 1958). The C_P/C_{Cr} ratio and the % T.R.P. $\left(=\left[1-\frac{C_P}{C_{Cr}}\right]\times 100\right)$ have been used to correlate the phosphate-clearance with G.F.R. Nordin and Fraser (1956) have related the clearance ratio to plasma-phosphorus as a P.E.I. It is generally agreed that these indices of phosphate-clearance measured at endogenous levels of plasma-phosphorus do not unequivocally distinguish patients with hyperparathyroidism. Thus we have found that the C_P/C_{Cr} ratio and P.E.I. were normal in two patients with hyperparathyroidism and abnormally high in one patient (case 12) with renal calculi, and one with inactive acromegaly (case 27).

McGeown (1957) reported similar findings of normal C_P/C_{Cr} ratios in three out of thirteen proven cases of hyperparathyroidism, all of which had normal renal function. These three patients and one other had a normal P.E.I. Normal values of phosphate-clearance in hyperparathyroidism have been described by Kyle et al. (1958) and normal % T.R.P.S have been reported by Goldman et al. (1957) and Thomas et al. (1958).

The converse finding of abnormal indices of phosphate-clearance in the absence of any other evidence of hyperparathyroidism has been described by Nordin and Fraser (1956) and McGeown (1957) in patients with renal calculi, and by Thomas et al. (1958) in patients with hypercalcæmia associated with myeloma or carcinoma.

Maximum Tubular Reabsorption of Phosphate

When the plasma-phosphorus level is progressively raised, the quantity of phosphorus reabsorbed by the renal tubule will theoretically reach a maximum (the Tm_P).

Anderson (1955b) and Thompson and Hiatt (1957) have suggested that the Tm_P is lowered in hyperparathyroidism. There is doubt, however, about the constancy of Tm_P measurements.

Anderson (1955a) demonstrated a Tm_P in six normal young adults studied carefully under basal conditions. On the other hand, Longson et al. (1956) found that in some subjects the phosphate reabsorption varied considerably during an infusion (perhaps because of alterations in G.F.R.), and also varied from day to day in any individual. Thompson and Hiatt (1957) describe similar findings, including changes possibly due to diet. In our own experience the Tm_P has shown considerable changes during fourteen out of twenty-one infusions, particularly in hyperparathyroid patients. This inconstancy has been noted with both inulin-clearance and creatinine-clearance as the measure of G.F.R.

It has been noted above that the results in two patients before and five months after parathyroidectomy were indistinguishable. Moreover there was no distinction between patients of group 1 (e.g., case 4) and other patients (e.g., cases 13 and 27). Reynolds et al. (1959) report similar findings in eight proven cases of hyperparathyroidism. Tm_P is clearly influenced by many factors, of which parathyroid function is only one, and it is therefore not the parameter of choice in assessing hyperparathyroidism.

Conclusion

In this investigation the theoretical renal phosphate threshold has been the most useful single parameter for assessing hyperparathyroidism. From the patients' point of view it is much quicker than studying the effect of low-calcium or low-phosphate intake, and it makes possible the investigation of inpatients within 24 hours.

Summary

The renal phosphorus threshold has been shown to be abnormally low in hyperparathyroidism, and it is of particular value in recognising hyperparathyroidism in patients who only have renal calculi. It may be abnormal when other parameters are normal.

Other indices of phosphate excretion, based on plasma-phosphorus levels, phosphate-clearance, or maximal tubular reabsorption of phosphate, are less valuable.

Our grateful acknowledgments are due to Mr. J. M. Pullan, who performed all the parathyroidectomies on the patients under our care; to Dr. H. K. Goadby for permission to study case 5; to Mr. R. H. O. B. Robinson and Mr. T. W. Mimpriss for permission to study some of the cases with renal calculi; and to Dr. J. Hawkins, Mr. R. Hurst, and the staff of the William Dunn laboratory for their technical assistance.

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CHOLESTEROL-BINDING CAPACITY OF SERUM GLOBULINS IN NORMAL AND ATHEROSCLEROTIC SUBJECTS

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WATER-INSOLUBLE hydrophobic cholesterol exists in a state of colloidal solution in biological systems. The colloidal cholesterol-containing aggregates are complex structures with respect to size, configuration, and composition. Their essential constituents are not only the plasma-lipids but also proteins—namely, α and β globulins (Chargaff 1944, Weinhouse 1943, Hueper 1945). Some qualitative alterations in the protein moieties of the cholesterol-containing micelles may occur, and this may influence atherogenesis (Katz and Stamler 1953). Indeed, electrophoresis (Barr et al. 1951) and ultracentrifugation (Gofman 1950, Gofman et al. 1950) have revealed such alterations in the lipid-containing micelles of the plasma.

On the other hand, electrophoretic and biochemical investigations on atherosclerotic intimas showed that the lipid-containing globulins of atheromatous plaques are not normal, and that the lipid-binding capacity of these globulins is increased (Kayahan 1959). This shows that proteins are important in the pathogenesis of atherosclerosis.

In atherosclerotic patients the absolute level of the blood-cholesterol is sometimes normal; but in people with high blood-cholesterol the incidence of atherosclerosis is high (Gubner and Ungerleider 1949, Gertler and Garn 1950). The purpose of this investigation was to determine the lipid-binding capacity of the serum globulins in normal subjects, in atherosclerotic patients with normal blood-cholesterol, and in patients with hypercholesterolæmia and arteriosclerosis.

TABLE I—LIPID BOUND BY 1 G. OF α-β GLOBULIN IN SERUM (MG. LIPID PER G. GLOBULIN)

Origin of serum		Cholesterol	Lipid
Atherosclerosis	Serum-cholesterol level		
Absent	Normal	98 (69–154)	472 (323–668)
Present	,,	102 (72–167)	496 (342–688)
,,	Raised	181 (165–263)	962 (743–1169)

Figures are means of 10 measurements with the ranges in parentheses.

Materials and Methods

The cholesterol, total lipid, and α and β globulins were estimated, and the cholesterol and total lipid contents of 1 g. of α-β globulin were calculated. The serum lipids were then extracted with ether. Electrophoresis showed that this had not denatured the serum proteins significantly. After the ether extraction, the total lipid and cholesterol remaining in the serum were estimated again. The lipid-containing ether was evaporated to dryness, and the lipid fractions were redissolved in the serum which was washed with ether. These mixtures were incubated at 37°C for 20 hours. They were then centrifuged at 3000 r.p.m. for 30 minutes, and the undissolved lipids were discharged. Electrophoresis revealed that the added lipids were bound again to α and β globulins.

The total lipid and cholesterol contents of the serum specimens were estimated again, and with these and previous values, the quantities of cholesterol and total lipid combined with 1 g. of α-β globulin were calculated.

Results

Table I shows the quantity of cholesterol and total lipid bound to 1 g. of α-β globulin in the serum of normal subjects and atherosclerotic patients. The values for normal subjects were 98 and 472 mg., and the corresponding values for patients with atherosclerosis and high serum-cholesterol level were 181 and 962 mg.

Table II shows the amount of cholesterol and total lipid combined with 1 g. of α-β globulin of the serum in four groups of experiments.

Conclusions

The tables show that there is considerable difference in the lipid-binding capacity of the serum globulins of normal subjects and of patients with hypercholesterolæmia and atherosclerosis. The serum globulins of the latter combine with twice the amount of lipids extracted from the serum of either atherosclerotic patients or normal subjects. The lipid-binding capacity of the serum globulins of normal subjects, on the other hand, is much less.

The serum globulins of patients with atherosclerosis and normal serum-cholesterol levels behave like those of normal subjects.

These results suggest that there are structural alterations of the serum globulins in patients with hyper-

TABLE II—CAPACITY OF SERUM GLOBULINS TO BIND SERUM LIPIDS (MG. LIPID BOUND BY 1 G. GLOBULIN)

Source of globulin		Source of lipid	Bound cholesterol	Bound total lipid
Atherosclerosis	Serum-cholesterol	Atherosclerosis		
Absent	Normal	Present	78 (49–95)	386 (224–507)
Present	,,	,,	82 (52–108)	402 (258–612)
,,	Raised	Absent	148 (113–195)	774 (612–964)
,,	,,	Present	172 (128–215)	802 (635–984)

Figures are means of 10 experiments with the ranges in parentheses.

cholesterolæmia. Electrophoresis and ultracentrifugation of the serum lipoproteins also support this view. On the other hand the lipid-binding capacity of the globulins of aortic intima has also been found to be increased in atherosclerosis (Kayahan 1959).

These findings support the view that the lipid-binding capacity of the globulins of the serum and intima may determine the plasma-lipid level and the lipid accumulation in atheromatous plaques of the intima, and that the metabolic changes of the lipid-binding globulins of the serum and intima may be of primary importance in the pathogenesis of atherosclerosis.

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A SINGLE-DOSE TREATMENT OF THREADWORMS IN CHILDREN

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A HIGH proportion of town-dwelling children are infected with threadworms ("pinworms") and the majority apparently have unimpaired health (White 1956). However, the *Enterobius vermicularis* occupies the cæcum and appendix, and its relation to appendicitis has long been debated.

That two common complaints may coexist is not surprising, but a causal relationship has not yet been firmly established, although Duran-Jorda (1957) provided good supportive evidence. In a careful histological study of 691 excised appendices, he found that the 52 which contained threadworms were all inflamed; and he also demonstrated that the enterobius invades the substance of the appendix, causing a breach of the mucosa which would theoretically permit the entry of intestinal bacteria. These findings accord with the views of Faust (1955), while Wilkinson (1959) believes that threadworm appendicitis is a clinical reality.

Most cases of enterobiasis are treated for æsthetic reasons or because of perianal irritation; but, from the above evidence, it is arguable that treatment is also justified as a preventive measure.

In treating enterobiasis with piperazine, White and Standen (1953a) achieved a cure-rate of 97%, using 50–75 mg. per kg. body-weight in divided daily dosage for seven days. In the case of ascariasis, it has been established that single doses of piperazine citrate, phosphate, and adipate, equivalent to 4 g. of piperazine hexahydrate, yield a cure-rate of over 80% (Goodwin and Standen 1958).

The action of piperazine has been studied by Standen (1955), who showed that pig roundworms, immersed in a modified Baldwin's solution containing a 1/560 concentration of piperazine citrate, were immobilised in six to twenty-four hours, yet continued to metabolise and recovered when removed and placed in a piperazine-free medium. Goodwin and Standen (1954) also observed that specimens passed after piperazine treatment in man recovered when incubated at 37°C in piperazine-free Ringer's solution. Since threadworms and roundworms are both nematodes it seems reasonable to suppose that the action of piperazine on both is similar.

Bumbalo et al. (1958) treated 37 infected children with a single dose of piperazine-citrate syrup (70 mg. per lb. body-weight, up to a maximum of 3 g.) but could achieve a cure-rate of only 43%. They later obtained cure-rates of 86% by giving a dose of 3 g., regardless of age, and repeating it after four days, and of 91% using a dose of 3 g. on three consecutive days.

Theoretically, the aim of treatment should be to maintain an adequate concentration of piperazine within the intestine long enough to ensure complete evacuation of all the paralysed worms by normal peristalsis. However, there is considerable individual variation in intestinal motility, and Bockus (1944) has shown that in some people complete elimination of waste food-products from the bowel may take as much as four days. In these "slow excretors" a single-dose treatment might fail, since parasites which have not been expelled may recover from the paralytic action of piperazine. This possibility was recognised by Standen (1955) who, when treating ascariasis with a single dose of piperazine citrate, recommended the use of a purge in costive patients. We thought that, in combination with a single dose of piperazine, standardised senna ('Senokot') would be more suitable than a saline purge, because its mode of action—namely, stimulation of muscular contraction of the colon through Auerbach's plexus—is physiological and reliable (Burgess 1958). Moreover, it is non-irritant (Douthwaite and Goulding 1957, Fairbairn 1958) and non-toxic (Hawkins 1958).

A palatable compound containing piperazine phosphate and standardised senna, in the form of flavoured granules ('Pripsen') was prepared and offered to us for evaluation. We could hardly hope to exceed the cure-rate of 97% previously attained; but we thought that, with this preparation, the length of treatment of enterobiasis might be reducible without prejudice to the results.

Investigation

Material and Methods

40 grains (2·6 g., approximately one-teaspoonful) of pripsen granules contain piperazine phosphate 1 g. and standardised senna equivalent to 7 mg. of sennosides A and B, in a flavoured base. The control preparation contained an equivalent amount of piperazine phosphate, but no senna; it was almost identical in appearance and taste. For the trial the two preparations were issued by the manufacturers in weighed doses, as compounds D and E, and their identity was not disclosed until the results had been analysed. With each preparation, children of 2–5 years inclusive received 120 grains (= 3 g. of piperazine phosphate) while those of 6–12 years received 160 grains (= 4 g.). It was felt that in practice this scheme would be simpler than one based on body-weight.

182 cases of enterobiasis were detected among medical and surgical admissions to the Evelina Children's Hospital, by identification of ova on adhesive 'Cellophane' swabs taken from the perianal region in the morning, before bathing and toilet (Graham 1941). Infected

children were treated alternately with compounds D and E, which were given at bedtime, accompanied by a drink or mixed with milk, water, or jam. Perianal swabs were then taken on ten successive days, beginning on the morning after treatment.

We considered that (1) the rate of disappearance of ova after treatment would indicate the rapidity with which worms were expelled; and (2) during the first ten days after treatment the results would not be prejudiced by autoinfection, since maturation from ovum to oviposition is believed to take four to six weeks.

Every slide was examined by an experienced technician and the appearance of one or more ova constituted a positive swab. The criterion of cure was seven negative swabs (Mac Keith and Watson 1948), which meant that any child showing a positive swab after the third day was counted a failure.

Results

In 60 cases the child was discharged from hospital before ten post-treatment swabs could be obtained, and these cases have been excluded from the trial. Of the 122 remaining for analysis, 59 had received pripsen and 63 piperazine phosphate alone. 57 (97%) of the former and 58 (92%) of the latter fulfilled the criteria for a cure (see table), and of the cured cases, those treated with pripsen showed a more rapid clearance-rate (see figure). These differences, though not statistically significant, are in the expected direction.

Side-effects

Of the children treated with pripsen, 4 vomited during or immediately after administration; 1 was afterwards found to be cured and 3 had to be excluded. The majority had one to four soft or loose motions next day but only a few complained of abdominal discomfort. We have met only one instance of frank diarrhœa, occurring in a 4-year-old boy (not included in this trial) who was accidentally given 320 grains of pripsen (= 8 g. of piperazine phosphate). He had completely recovered within twenty hours. One child who received the control preparation had transient diarrhœa and vomiting and another complained of nausea. On the whole both compounds were readily accepted by most of the children, and no systemic toxic effects were observed.

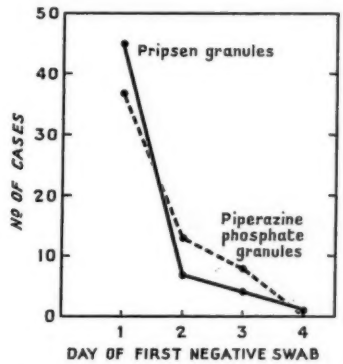
Discussion

These results show that a high cure-rate of enterobiasis can be achieved with a single dose of pripsen. Since, however, Bumbalo et al. (1958), using a single dose of piperazine-citrate elixir, had a cure-rate of only 43%, we were somewhat astonished to find that in our control group, treated with granules of piperazine phosphate alone, the corresponding rate was 92%. With a dose of 70 mg. per lb. body-weight and a maximum of 3 g., some of Bumbalo's cases almost certainly had a slightly smaller total dose than ours; but this may not be the full explanation of the wide discrepancy. Standen (1955) found no difference in the in-vitro activity of piperazine citrate and phosphate solutions; but it is conceivable that the granular preparations used in the present trial may have physical properties which retard absorption from the alimentary tract and thus favour the maintenance of a higher concentration in the large bowel. The absorption and excretion rates of this particular preparation have not yet been studied.

PERCENTAGE CURES

Treatment	Number of cases			% cures
	Total	Failures	Cures	
Pripsen	59	2	57	97
Piperazine phosphate ..	63	5	58	92

While the majority of the cured children showed no positive post-treatment swabs, a number gave positive swabs for one, two, or (in 1 case only) three days. During this time some of these children must become reinfected, and treatment should therefore be repeated, the best time for repetition probably being one or two weeks after the initial treatment. With single-dose treatments the toxic effects sometimes described during seven-day courses (Sims 1953, White and Standen 1953b) have not been seen by either Bumbalo et al. (1958) or ourselves. In our trial the total dose of piperazine used in each child was less than half that hitherto used in a seven-day course.



The rate of clearance as indicated by the day on which the first of seven or more negative swabs was found.

With its high cure-rate, lack of toxicity, ease of administration, and simplicity of dosage, we regard pripsen as, at present, the remedy of choice for enterobiasis. Fuller studies are needed, however, to determine the precise role of its senna component and also the pharmacological properties of the granular form in which the piperazine phosphate used in our trial was presented.

Summary

For treatment of threadworms the results obtained in 59 children given 'Pripsen' (a new granular compound containing piperazine phosphate and standardised senna) are compared with those obtained in 63 children given piperazine phosphate alone. Though both preparations were given as single doses, the cure-rates were much the same as those reported with seven-day courses of piperazine.

The doses of piperazine were less than half those hitherto used in seven days' treatment, and there were no toxic effects.

Using a single dose of piperazine-citrate elixir, Bumbalo et al. (1958) had a much lower cure-rate; and further work is needed to elucidate the possible pharmacological advantages of the granular preparation of piperazine phosphate, as well as the precise part played by the senna component.

We wish to thank the consultant staff of the Evelina Children's Hospital for allowing us to treat their patients, the nursing staff for their constant help, and Mr. F. J. Gibbs for examining the slides. The pripsen and piperazine-phosphate granules were supplied by Westminster Laboratories Ltd.

(*References overleaf*)

BIOCHEMICAL NORMALS IN NIGERIANS
URINARY 17-OXOSTEROIDS AND 17-OXOGENIC STEROIDS

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IN the course of routine analyses of urine from Nigerian patients at University College Hospital, Ibadan, it was observed that the urinary 17-oxosteroid excretion per 24 hours was significantly lower than values quoted in the literature and lower than was found in European patients. In view of the increasing importance attached to the study of adrenal cortical hormones, it seemed desirable to find out the significance of these low values. Assays were accordingly made on the urine of healthy Nigerian adults in order to establish normal values with which to compare the figures obtained from abnormal urine. The results of this survey are here reported.

Materials and Method

The subjects studied included forty-five male and fifty-five female Nigerians aged 20–30.

Twenty of the males were laboratory staff (two doctors and eighteen student laboratory technologists). The other twenty-five males were labourers. Thirty of the females were student nurses resident in the nurses' home at University College Hospital, Ibadan, while the other twenty-five were relations or wives living with the twenty males mentioned above. The 24-hour urine samples were collected into Winchester bottles containing 10 ml. of concentrated hydrochloric acid as preservative. Creatinine excretion was measured in all the urine samples; only three showed a creatinine output of less than 1 g. per 24 hours, and these were excluded from the series. As a check on the methods, urine samples of six healthy male European laboratory technologists, aged 25–30, working at University College Hospital, Ibadan, were also analysed.

Urinary 17-oxosteroids were determined by the method described by Moxham and Nabarro (1956). The 17-oxogenic steroids were estimated by Moxham and Nabarro's (1956) modification of the method of Appleby et al. (1955), in which the pre-existing oxosteroids are destroyed with sodium borohydride, and the glucocorticoids are then oxidised with sodium bismuthate. For the determination of creatinine in urine the alkaline-picrate method of Bonsnes and Taussky (1945) was used.

Results

The mean 24-hour urinary output of the six Europeans was 16·5 mg. for 17-oxosteroids and 15·4 mg. for 17-oxogenic steroids. These figures are near the values given by other workers (Barnett et al. 1946, Moxham and Nabarro 1956). The urinary 17-oxosteroids and 17-oxogenic steroids in the Nigerians are presented in table I; adult males excreted about 50% more 17-oxosteroids than adult females. The output of 17-oxogenic steroids was only slightly higher in males than in females (10%). The urinary output of 17-oxosteroids and 17-oxogenic steroids was about 35% lower in Nigerians than in healthy adult Europeans of comparable age. This was seen in each sex.

TABLE I—URINARY STEROID EXCRETION IN ADULT NIGERIANS (as mg. per 24 hours)

Males:	
17-oxosteroids	10·1 ± 3·2 (4·1–20)
17-oxogenic steroids	10·6 ± 2·7 (5·3–18·9)
Females:	
17-oxosteroids	7·2 ± 2·7 (4·0–15·0)
17-oxogenic steroids	9·7 ± 2·0 (6·5–15·0)

To determine whether this difference has racial background or whether it depends on socioeconomic factors, the Nigerian results were analysed into two income groups. The results are shown in table II. Group M_1 comprises the twenty male laboratory workers and M_2 the twenty-five male labourers. F_1 comprises thirty student nurses, and F_2 the relatives and wives of group M_2. In both males and females, improvement in economic means produced significant increase in the mean urinary output of 17-oxosteroids and 17-oxogenic steroids. The urinary excretion of 17-oxosteroids correlated more closely with income than did the urinary 17-oxogenic steroids. The effect of nutrition was further demonstrated by measuring the 17-oxosteroid excretion in a male nephrotic at various levels of protein intake. The dietary protein was changed weekly, and urine for steroid analysis was collected on the 6th and 7th days at each level of protein intake. The results are shown in table III.

TABLE II—EFFECT OF INCOME ON THE URINARY STEROID EXCRETION OF NIGERIANS

17-oxosteroids (mg. per 24 hours)		17-oxogenic steroids (mg. per 24 hours)	
M_1	M_2	M_1	M_2
12·7 ± 3·8	8·3 ± 1·7	12·1 ± 3·7	9·4 ± 1·6
$0{\cdot}001 > P$		$0{\cdot}01 > P > 0{\cdot}001$	
F_1	F_2	F_1	F_2
8·5 ± 2·8	5·8 ± 1·0	11·1 ± 3·1	9·1 ± 1·2
$0{\cdot}001 > P$		$0{\cdot}01 > P > 0{\cdot}001$	

Discussion

Barnicot and Wolfsson (1952) also found low urinary 17-ketosteroid-levels in Nigerians (average excretion 7·97 ± 0·48 mg. per 24 hours), and there was no difference between Nigerian students resident in London and a group of Nigerian labourers working at Oshodi. Friedman (1954) and Ramachandran et al. (1956) reported low values for Indian adults, and Lugg and Bowness (1954) found similar low values for Malayans in Malaya. It is significant that all these people lived in areas of endemic undernutrition, especially as regards protein.

The urinary neutral 17-oxosteroids reflect androgenic

TABLE III—EFFECT OF PROTEIN INTAKE ON THE 17-OXOSTEROID EXCRETION OF A MALE NEPHROTIC

—	Dietary nitrogen (g. per 24 hours)	Urinary 17-oxosteroids (mg. per 24 hours)
1st week:		
Oct. 16–17	4·9	3·7 } Average 3·6
„ 17–18		3·5 }
2nd week:		
Oct. 23–24	15·2	5·0 } Average 5·5
„ 24–25		5·9 }
3rd week:		
Oct. 30–31	23·6	7·7 } Average 8·0
„ 31–Nov. 1		8·2 }
4th week:		
Nov. 6–7	32·0	8·7 } Average 8·5
„ 7–8		8·2 }

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functions; in the female they are produced entirely by the adrenal cortex, and in the male by the adrenal cortex and testes. The testes contribute a third of the neutral urinary 17-oxosteroids. The androgenic hormones have important metabolic effects, causing retention of nitrogen and phosphorus. The urinary 17-oxogenic steroids measure the excretion of 17-hydroxycorticosteroids, which are important in the metabolism of protein, carbohydrate, and fat. In view of the role of the adrenal hormones in metabolism, it is not surprising that the production of these hormones, and hence the excretion of their metabolites, is in some way related to the nutritional state.

It has been suggested that the low steroid excretion in Africans is due to poor liver function and consequent failure to convert androgenic hormones efficiently into neutral 17-oxosteroids. But a recent survey (Edozien 1958) revealed no evidence of impairment of liver function in apparently healthy Nigerians. Further, Barnicot and Wolfsson (1952) found no significant difference in the mean values for the recovery of testosterone in Africans and Europeans. The alternative explanation suggested by my data is that a dynamic relation exists between the level of food intake—and particularly protein—and the production of adrenal hormones.

Summary

Urinary 17-oxosteroids and 17-oxogenic steroids in Nigerians have been studied. The mean excretion per 24 hours of 17-oxosteroids and 17-oxogenic steroids was lower than in Europeans.

Among the Nigerians the urinary steroid excretion varied according to the socioeconomic background. This should be borne in mind in evaluating the results of urinary steroid analyses in Africans and other subjects from areas of endemic undernutrition.

I wish to thank Mr. J. M. Pescod, F.I.M.L.T., for technical assistance; Miss L. Bell, principal sister-tutor, University College Hospital, Ibadan, and Dr. D. Mendel, of the department of physiology, University College, Ibadan, for their cooperation over the samples; Dr. Mendel for the figures for nitrogen intake from the nephrotic patient.

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ALDOSTERONE AND HYDROCORTISONE SECRETION IN DEHYDRATION

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OLIGURIA or, in more severe cases, azotæmia is known to occur in dehydration. As we have shown, both hæmodynamic and tubular factors contribute to the impairment of renal function. As a result of the fall in blood-pressure and of concentration of the plasma (i.e., increased colloid osmotic pressure) the filtration pressure in the glomeruli decreases (Gömöri 1954, Gömöri and Podhradszky 1937, Gömöri et al. 1939, Margitay-Becht and Gömöri 1938). The reduction of glomerular filtration can clearly be shown by the clearance method (Gömöri 1954, McCance and Widdowson 1937, Margitay-Becht and Gömöri 1938, Takács and Kállay 1957). The slowing of the circulation in dehydration is obviously followed by reduction of the blood-supply to the kidneys and deterioration of their function (Gömöri 1954, Gömöri et al. 1939, Takács and Kállay 1957). At the same time tubules undergo anatomical changes which lead to the " passive " rediffusion of urea (Gömöri et al. 1949, 1954, Kenney 1949).

The question might arise whether humoral factors also contribute to the development of oliguria in dehydration. We have shown that antidiuretic-hormone activity does not increase in dehydration, and thus increased antidiuretic-hormone activity is unlikely to be a factor (Gömöri, Varga, and Jakab 1958). On the other hand, we have shown (Gömöri, Gláz, et al. 1958) by biological methods (Tait et al. 1952) in dogs that, in dehydration following obstruction of the pylorus, aldersterone-like activity greatly increases in the blood of the adrenal-gland veins. This increase may explain the reduction of sodium excretion—i.e., oliguria. Using likewise biological methods, Luetscher and Curtis (1955) found increased aldosterone-like activity in the urine of a patient with pyloric stenosis; and Bartter et al. (1956) recorded this finding in patients with reduced salt intake and induced thirst. According to these workers, reduction of extracellular space leads to the increase of aldosterone-like activity.

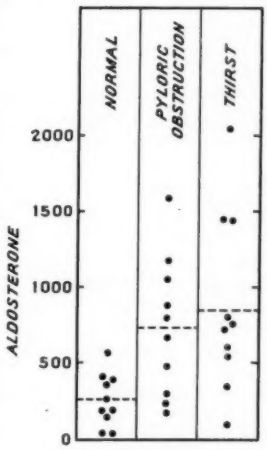

Fig. 1—Aldosterone (μg. per hour per g. adrenal weight per kg. body-weight) in adrenal venous blood in three groups of dogs: normal, with pyloric obstruction, and with induced thirst.

Because the biological method is essentially based on the detection of a salt-retaining factor, it seemed desirable to determine both aldosterone and hydrocortisone in dehydration by quantitative chemical analysis.

Accordingly we induced dehydration in dogs by obstructing the pylorus, as in our previous experiments (Gömöri and Podhradszky 1937, Gömöri et al. 1939, 1954, Gömöri, Gláz et al. 1958, Gömöri, Varga, and Jakab 1958), while another group of dogs was starved of food and water for 48 hours. After 48 hours aldosterone and hydrocortisone were estimated in the blood of the adrenal glands. In order to determine hormone secretion, the dogs were treated with heparin and were anæsthetised with chloralose. Adrenal venous blood was collected by cannulating the left adrenolumbar vein with a polyethylene catheter located peripherally at the point of venous inflow from the left adrenal gland. All tributaries to the adrenolumbar vein in this region—other than the adrenal veins—were ligated, and the adrenolumbar vein was obstructed at its junction with the inferior vena cava. By this procedure the flow of venous blood from the left adrenal gland was diverted from its normal path into the catheter.

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The heparin-containing plasma thus obtained was extracted with ethyl acetate and, after alkali purification, shaken from a petrol-ether solution into 70% alcohol. Aldosterone was isolated chromatographically, starting with the dried residue of the alcoholic extract. Chromatography was carried out by the method of Moolenar (1957) in two systems on Whatman no. 1 paper. Chromatography was followed by development with tetrazolium-blue; the developed formazon spots were eluted, and quantitative determination was carried out with a Beckmann B spectrophotometer.

Observations were on ten control dogs. Ten dogs were kept off water; and ten further dogs had their pylorus obstructed before the experiment.

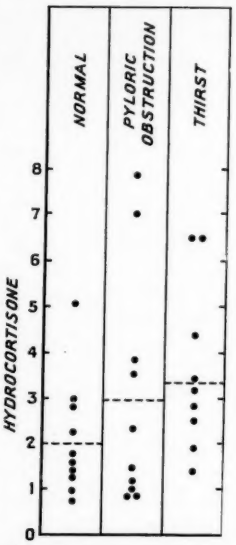

Fig. 2—Hydrocortisone (μg. per hour per g. adrenal weight per kg. body-weight) in venous blood from adrenal gland in three groups of dogs: normal, with pyloric obstruction, and with induced thirst.

Our results showed that there was a considerable increase in aldosterone secretion in most of the dogs in which the pylorus had been obstructed, as in most of the dogs simply deprived of food and water, as compared with the secretion of the control dogs (figs. 1 and 2). Statistical calculations show that the change is significant ($P < 0.01$). The increase in hydrocortisone is less unequivocal; the change cannot be termed significant ($P > 0.05$, Student test).

Our experiments indicate that increased aldosterone secretion is a factor in the reduced excretion of sodium in conditions of dehydration.

Summary

Aldosterone secretion in the blood of the adrenal glands of dogs increased after obstruction of the pylorus or induction of thirst. The change in hydrocortisone secretion was not significant.

We wish to thank Miss Maria Paul for her kind assistance in carrying out the technical work.

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" . . . Medicine will become during the next ten years a more and more exact science . . . The trend towards an increasing number of examinations using complex apparatus is bound to increase the cost of the health services. Countries like the United Kingdom which enjoy a National Health Service must accept the idea that within the next ten years, real costs will be doubled, perhaps trebled."—Prof. ZENON M. BACQ, *New Scientist*, Jan. 21, 1960, p. 128.

CHOLINE THEOPHYLLINATE IN CHILDREN WITH ASTHMA

A CONTROLLED TRIAL

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ASSESSING the effectiveness of treatment in asthma is difficult because of the many variables which may influence the condition. Hence objective methods are necessary to measure the value of antispasmodic drugs.

In a study of children with chronic pulmonary diseases (Strang 1960) it was shown that the ventilatory capacity in terms of the forced expiratory volume in 1 second ($F.E.V._1$) provided a satisfactory measurement of the asthmatic child's disability. It was also shown that in the severe asthma of childhood, a persistent abnormality may exist over many months, and that asthmatic attacks more often arise as exacerbations of a subacute or chronic condition than they do from a previously normal ventilatory state. The studies by Kennedy and Thursby-Pelham (1956, 1958) of the ventilatory capacity of asthmatic children during treatment with cortisone and prednisone revealed a similar kind of persistent impairment.

In view of these findings, it seems reasonable to base the treatment of severe asthma on long-continued daily administration of drugs which reduce bronchial obstruction and improve the ventilatory capacity. Gagliani et al. (1954) and Turner-Warwick (1957) have shown that choline theophyllinate produces adequate blood-levels of theophylline after oral doses, and that the levels are at least as good as those produced by other theophylline compounds.

TABLE I—FAILURES TO ATTEND FOR EXAMINATION

Reason for failure	Lactose	Choline theophyllinate
Apparatus not available	2	11
Holidays	2	6
Illness	2	4
Total	6	21

An investigation of antispasmodic drugs by Gandevia et al. (1957) showed that choline theophyllinate was effective in improving ventilatory capacity. It causes less gastric irritation than aminophylline, and it has been suggested that it is most effective when administered over a long period (Dann et al. 1954, Brown and Glancy 1955). We decided, therefore, to conduct a controlled trial of this drug, to measure its effect on the ventilatory capacity of children with severe asthma, when given four times daily for a prolonged period.

The Trial

Fourteen children aged 7–13 years took part in the trial. All were regarded as severe asthmatics and their parents said they were having attacks at least once every 4 weeks. During the trial it became evident that most of them had a persistently impaired ventilatory capacity. The trial started in September, 1958, and ended in February, 1959.

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TABLE II—CHEST SIGNS ON AUSCULTATION DURING TREATMENT WITH LACTOSE AND CHOLINE THEOPHYLLINATE

Chest signs	Lactose	Choline theophyllinate
Present	48	29
Absent	42	46

$\chi^2 = 2{\cdot}971$; $P > 0{\cdot}05$.

Seven children were given 1 lactose tablet four times daily for 3 months, followed by 1 tablet of choline theophyllinate four times daily for 3 months. The other seven children started with choline theophyllinate for 3 months, and then continued with lactose tablets for 3 months. The children were allocated at random to these two groups, and the investigator who saw them did not know whether they were having lactose or the trial drug.

The dose of choline theophyllinate was 0·1 g. for children under 10 years, and 0·2 g. for children of 10 years and over. The tablets were not identical in appearance, and the parents were told that the child was to have periods on two different drugs to find out which was better. The parents were also supplied with ephedrine tablets (gr. $^1/_2$) 1 of which was to be given if the child had an attack of asthma requiring treatment.

TABLE III—DYSPNŒA ON EXERTION DURING TREATMENT WITH LACTOSE AND CHOLINE THEOPHYLLINATE

Dyspnœa	Lactose	Choline theophyllinate
Present	44	30
Absent	46	45

$\chi^2 = 0{\cdot}972$; $P > 0{\cdot}05$.

All the children were seen at 14-day intervals, but twenty-seven of the planned examinations were missed for various reasons. Each time the F.E.V.$_1$ was measured, the chest was auscultated for the presence or absence of rhonchi, and a note was made of the number of attacks of wheezing and the presence or absence of dyspnœa on exertion.

Results

Table I shows the numbers of planned examinations which were missed in each treatment group. The difference between the two groups was largely due to the spirometer not always being available.

Clinical Data

At the end of the trial five patients thought that choline theophyllinate was more effective, two thought lactose was more effective, and seven thought there was no difference. The number of attacks of asthma in the two groups was compared by calculating the differences in the mean numbers of attacks per visit for each child in the two periods. The mean difference was 0·43 attacks more in the lactose periods, and this did not differ significantly from zero ($t = 0{\cdot}322$, $P > 0{\cdot}05$). The frequency of rhonchi was not significantly different in the two groups (table II), nor was the frequency of dyspnœa (table III). No symptoms due to drug toxicity were observed.

Ventilatory Data

The F.E.V.$_1$ results, converted to a percentage of the normal for height (Strang 1959), are presented in table IV. They were treated by analysis of variance in two stages.

The first form of analysis (table V) extracted from the total variation that due to the method of treatment, that due to the order of treatment, and that due to interaction between order and treatment. The variance-ratio test showed a significant benefit from treatment with choline theophyllinate. It also showed that the effect of order was not significant, the performances in both periods being similar. Finally, the order in which the drugs were given had no significant effect upon the response.

Because of the absence of order effect it seemed justifiable to ignore order. The data were then reanalysed in a manner which would show any heterogeneity among the children in their reactions to the drug, and separate this from variation between individual mean performances. This analysis, presented in table VI, shows that almost all the heterogeneity among children was due to variation between their mean performances, and that their responses to treatment were not significantly heterogeneous.

Ten of the fourteen children had better mean performances with choline theophyllinate than with lactose.

TABLE IV—SUCCESSIVE READINGS OF F.E.V.$_1$ AS % OF NORMAL FOR HEIGHT IN EACH TREATMENT PERIOD

Case no.	First 3-month period		Second 3-month period	
	Lactose	Mean	Choline theophyllinate	Mean
1	63, 64, 51, 53, 66, 68	57·5	82, 68, 50, 50, 73, 75	66·3
3	78, 71, 90, 65, 63, 60	71·2	69, 34, 29, 74, 77	56·6
5	51, 55, 81, 59, 50, 70, 67	61·9	85, 27, 61, 55, 68, 72	61·3
7	78, 99, 97, 50, 74, 90, 72	80·0	100, 76, 85, 75, 82	83·6
9	55, 56, 62, 41, 51, 60, 74	57·0	63, 81, 85, 75, 82	83·6
11	66, 32, 79, 40, 88, 64, 88	65·3	67, 88, 97, 88	85·0
13	22, 35, 34, 35, 21, 35, 43	32·1	82, 39, 45	55·3
		60·6		69·1
	Choline theophyllinate	Mean	Lactose	Mean
2	72, 59, 36, 47	53·5	50, 32, 45, 44, 56, 59, 17	43·3
4	113, 113, 110, 111, 111, 32, 104	99·1	120, 121, 124, 110, 121, 127	120·5
6	30, 47, 45, 45, 46	42·6	32, 36, 37, 41, 31, 23, 38	34·0
8	77, 79, 91, 89, 73	81·8	83, 85, 61, 60, 89, 91	78·2
10	69, 49, 64, 53	58·8	44, 58, 63, 63, 56, 54	56·3
12	63, 59, 61, 33, 60, 44, 35, 65	52·5	65, 64, 48, 61, 52	58·0
14	38, 34, 54, 43, 31, 46	41·0	40, 36, 40, 35, 38, 45	39·0
		62·3		60·3

Mean F.E.V.$_1$ (% normal) first period (both treatments) = 61·4
" " " " second " " " = 64·3
Mean F.E.V.$_1$ (% normal) choline theophyllinate (both periods) = 65·6
" " " " lactose " " = 60·5

TABLE V—ANALYSIS OF VARIANCE (1)

Source of variation	Sums of squares	Degrees of freedom	Variance estimate	Variance ratio (F)	P
Between treatments ..	1067	1	1067	5·45	<0·025
Between periods ..	360	1	360	1·84	>0·05
Interaction between treatments and periods	485	1	485	2·47	>0·05
High order interaction and variations between children	63,795	24	2658	13·58	<0·01
Residual	26,810	137	196	..	..
Total	92,517	164	..	..	..

TABLE VI—ANALYSIS OF VARIANCE (2)

Source of variation	Sum of squares	Degrees of freedom	Variance estimate	Variance ratio (F)	P
Between treatments ..	1067	1	1067	5·45	<0·025
Between Children ..	59,698	13	4592	23·46	<0·001
Interaction between children and treatments	4941	13	380	1·94	>0·05
Residual	26,810	137	196	..	..
Total	92,517	164	..	..	..

Discussion

Analysis of the symptoms indicated some benefit from choline theophyllinate compared with lactose, but the

differences were not statistically significant nor were the children's parents strongly in favour of one or the other. The ventilatory data, however, clearly showed benefit from choline theophyllinate; this was independent of the order in which the drugs were given, and, therefore, of changes in weather and patterns of respiratory infection during this period. The response to treatment was reasonably uniform despite considerable variations in severity.

The measurement of ventilatory capacity at regular fortnightly intervals provided a representative sample of a fluctuating condition. Failure of patients to attend for these examinations could bias the samples, but in the present investigation the failures to attend were almost entirely due to chance factors, and are unlikely to have influenced the result.

The difference between the mean F.E.V.$_{1}$s of children on lactose or on choline theophyllinate was significant but disappointingly small, and these children seem to need additional treatment of some kind. We intend to assess other antispasmodic drugs and therapeutic procedures by a similar method. Nevertheless, we may conclude that choline theophyllinate is an effective therapeutic agent although the benefit is small.

Summary

As measured by the forced expiratory volume in 1 second, the ventilatory capacity of a group of fourteen children with asthma was altered favourably by the daily administration of choline theophyllinate.

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MEPHENESIN POISONING

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WE describe here the clinical features and management of a patient who took an overdose of mephenesin.

A housewife, aged 43 years, was admitted to hospital at 1 A.M. on Sept. 5, 1957, as an "emergency", having been found unconscious at home one hour before. Respiratory paralysis was diagnosed, and it was subsequently ascertained from her doctor that she had been given mephenesin ('Elixir Myanesin') some days previously on account of a chronic anxiety state. The patient had taken an overdose, but the exact quantity could not be determined. It was certainly not more than 6 fl. oz. and probably not less than 3 fl. oz., so that the total mephenesin taken was somewhere between 5·5 and 11 g. (She weighed 107 lb. [48·7 kg.].) She was not receiving any other medication at this time. Six months previously she had taken an overdose of barbiturates, since when these drugs had not been available to her.

The patient was comatose, but strong supraorbital pressure produced a slight response. Respiration was abdominal and diaphragmatic, with intercostal paralysis. Contraction of the accessory muscles of respiration was pronounced, the arms moving convulsively with each inspiratory effort. Cyanosis was evident, and pharyngeal and tracheal secretions audible. The blood-pressure was 110/80 mm. Hg, pulse-rate 116 and regular, temperature 97° F. The heart sounds were normal. The pupils were moderately contracted and reacted to light; tendon reflexes were present in the lower limbs and not exaggerated; the plantar responses were extensor. A catheter specimen of urine contained no glucose, acetone, albumin, or hæmoglobin.

Management

The patient was taken to the operating-theatre, where tracheobronchial toilet was carried out and a cuffed orotracheal tube inserted without difficulty. The cuff was then inflated and the tube connected to the "closed" circuit of an anæsthetic machine. Assisted respiration was carried out using 2 litres of nitrous oxide to 3 litres of oxygen, with carbon dioxide absorption and a "spill-over".

As soon as good oxygenation was obtained, a large-bore œsophageal tube was passed into the stomach and gastric lavage carried out with normal saline solution.

Assisted respiration was necessary for more than two hours. At 3.20 A.M. the intercostal muscles began to work and breathing became less laboured. Accessory muscles were no longer being employed, and the colour remained good.

The patient, still unconscious, was now disconnected from the anæsthetic machine; but the cuffed endotracheal tube remained in situ, tracheobronchial toilet being required occasionally.

This state of affairs persisted for a further seven hours, during which respiration was adequate and the patient gradually emerged from coma. At the end of this period—i.e., ten hours after the ingestion of the drug—the patient resented the presence of the endotracheal tube. Following removal of the tube she was awake and would obey commands in a slow lethargic manner. Over the next two hours she gradually became mentally alert and had no memory of events since the previous evening. There were moist sounds throughout both lungs which cleared up in two days with penicillin and physiotherapy. She was discharged from hospital on the fifth day, and has remained well ever since.

Discussion

Goodman and Gilman (1955) state that the incidence of serious untoward effects caused by mephenesin is low. They list the toxic effects as nystagmus, diplopia, lassitude, weakness, muscular incoordination, nausea, vomiting, syncope, sedation, and respiratory depression. Intravenous administration may cause phlebothrombosis, hæmolysis, hæmaturia and even anuria. Robson and Keele (1951) cite several workers who have shown that mephenesin has a short duration of action because it is rapidly oxidised. They state that in the rabbit very large doses cause paralysis of all muscles except the diaphragm. Gray (1954) also mentions that very large doses in animals produce narcosis. Goodier and Goodhart (1949) used a total of 39 ml. of 2% mephenesin during a partial gastrectomy, and found that relaxation was never satisfactory.

It would appear from this case that overdosage of mephenesin may produce more profound respiratory depression and sedation than has been supposed. As it is being increasingly recommended for common conditions, such as anxiety, tension states, and insomnia, it should be borne in mind as a possible cause in the differential diagnosis of respiratory depression or paralysis.

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Preliminary Communication

BENCE JONES PROTEIN OF MYELOMA

THIS communication describes an observation on the atypical proteins associated with myelomatosis (Bence Jones proteins).[1]

Because of the shortcomings of the various heating and salt-precipitation tests for demonstrating the presence of these proteins, it is now common practice to separate the urine proteins by paper electrophoresis. When the proteins have been separated and the paper strip is stained by the methyl-green/pyronin method of Trevan and Sharrock [2] for ribonucleic and desoxyribonucleic acid, a deep reddish-purple band is found at the site of the abnormal globulin. Such a band has been demonstrated in 11 proven cases of myelomatosis. In all these cases a positive staining reaction was obtained in both serum and urine. For these studies the amount of serum seeded on to the filterpaper was 0·010 ml. When investigating urine samples it was found necessary to vary the amount of urine in order to obtain a well-stained band, using the usual protein-staining agent (azocarmine B[3]): generally 0·025 ml. of urine was sufficient, but occasionally it was necessary to increase this to 0·050 ml. The urine specimens were not subjected to concentration by dialysis, but were seeded directly on to the filterpapers.

The reaction has proved to be negative in about a hundred other electrophoretic preparations from cases of hyperglobulinæmia and proteinuria not associated with myelomatosis. These sera were derived from cases of liver disease, collagen diseases, renal abnormalities, and various malignant tumours. The specimens of urine were from cases with proteinuria ranging from simple albuminuria to the more complex protein losses associated with advanced nephrosis.

I suggest that the method of Trevan and Sharrock may be specific for true myeloma protein.

My practice is to make three electrophoretic preparations. In two the serum and urine are treated separately, and in the third the urine is seeded on top of the serum on the paper strip. This method permits easy comparison of the respective mobilities of the various proteins in serum and urine.

Further investigations are being made of the staining material associated with the atypical globulins, particularly with regard to its staining behaviour in the presence of nucleases.

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1. Bence Jones, H. *Phil. Trans.* 1848, p. 55.
2. Trevan, D. J., Sharrock, A. *J. Path. Bact.* 1951, **63**, 326.
3. Yeoman, W. B. *Clin. chim. acta*, 1959, **4**, 523.

Reviews of Books

Brucella Infection and Undulant Fever in Man

Sir WELDON DALRYMPLE-CHAMPNEYS, C.B., D.M., F.R.C.P., late deputy chief medical officer, Ministry of Health; chairman, joint F.A.O./W.H.O. expert committee on brucellosis. London: Oxford University Press. 1960. Pp. 196. 25*s*.

Brucellosis in England

HUGH R. E. WALLIS, M.D., M.R.C.P., consultant pædiatrician, Bath clinical area. London: A. S. O. O'Connor. 1959. Pp. 140. 25*s*.

IT was over thirty years ago that Sir Weldon was instructed by the Chief Medical Officer at the Ministry of Health to inquire into the occurrence of undulant fever in England and Wales. Since that time he has read almost every word on the subject in many languages, he has talked to everyone who has a concern for this disease, and he has himself collected the available information on over 1500 indigenous cases. His findings and conclusions are now published in a small and elegant monograph. Here, without a wasted word, is all that anyone could reasonably want to know about a disease which may play only a small part in the Bills of Mortality but which remains of exceptional interest. This is not, we hope, the last word from this source, but it is a good foundation on which to base further inquiries.

Dr. Wallis' book is less ambitious. He records his observations on 42 patients whom he suspects have had undulant fever and draws some dogmatic conclusions. The clinical descriptions are interesting. Some of his patients undoubtedly suffered from undulant fever, but many physicians will be unconvinced by his diagnosis in at least half of the patients. As Sir Weldon points out, the diagnostic value of a rise in the titre of agglutinins after an injection of brucellin is doubtful: the same phenomenon can be demonstrated in some apparently normal subjects. Therapeutic success is a dangerous diagnostic weapon, as the author admits, but some of his diagnoses seem to depend on little else.

In spite of these two books there is still a great deal to be known about this disease. About 1% of the adult population show agglutination titres of 1/160 or more: it is easy to guess that these are the result of past infections but of this there is no proof. It would seem dangerous to make the diagnosis (*a*) in the absence of other signs and symptoms, and (*b*) without either a demonstrated rise in titre or the cultivation of the organism from blood or marrow. It is possible that today milk-borne infections are the exception. Most urban milk is pasteurised. In one dairying district more than 70% of proven cases of undulant fever in the past ten years have been in those doing bovine midwifery (and these make up only 1–2% of the population). Of course they all drink raw milk—and so do 50% of the rest of the rural population—but on the farm undulant fever is a disease of the adults rather than of the children. It is indeed so much of an occupational disease that some form of specific immunisation might be of value.

There has recently been some alarm about the occurrence of infection with *Brucella melitensis* in cattle in England. It has not so far been transmitted to man and appears to produce a disease in cows indistinguishable from that caused by *Br. abortus*. To the bacteriologist the three species of brucella are distinct entities, but in fact aberrant and intermediate types occur not uncommonly. It is possible that had his material been drawn from other places the bacteriologist's classification might have been different. It has been general experience that Malta fever (due to *Br. melitensis*) is a more severe infection in man than undulant fever caused by *Br. abortus*. It is conceivable that the distinction depends not upon the bacterial species but upon some biological differences in the parasite which have so far escaped notice. Does passage through the goat enhance bacterial virulence? Does the severity of infection depend upon the dose received? And, for that matter, what is the minimum infective dose for man?

Horses are now luxuries and therefore denied the benefits of veterinary science enjoyed by cows and other useful animals. Before it is too late someone should investigate the curious story that *Br. abortus* is the principal cause of poll evil and fistulous withers in horses—i.e., deep-seated and chronic abscess formation. Generally speaking, the pathological changes produced by natural infection with a bacterial parasite are much the same in all mammals. On the effects of S19 vaccine Sir Weldon is, perhaps, less than fair. Its introduction has certainly not yet reduced the number of human infections markedly; but the scheme is voluntary and even now less than half the calves born are inoculated. Since a cow remains a

useful source of milk for many years, the effects of calfhood vaccination are not likely to be dramatic. What is certain is that the number of abortions has fallen to less than a quarter, and it is said that at the moment less than 5% of the herds in the country are infected.

There is a lot to be learned from both these books—even if it is how little we know about a widespread disease.

The Clinical Syndrome of Diabetes Mellitus

JOHN LISTER, M.D., M.R.C.P., consultant physician and physician in charge of diabetic clinics, Windsor group of hospitals. London: H. K. Lewis. 1959. Pp. 234. 35*s*.

THIS book fills a gap in the literature on diabetes mellitus, for it deals with the subject in enough detail to cover interestingly most facets of the syndrome and yet its size is limited to just over 200 smallish pages. The script is enriched by a number of illustrations and photomicrographs, and there is a good brief historical introduction. Unfortunately there are also quite a number of inaccuracies and several omissions: sulphonamides are not mentioned for the treatment of urinary infections, and the recommendations for intravenous therapy after surgery could lead to gross overloading with saline. Good bibliographies are supplied with each chapter, although they include by no means all the references cited in the text. The book can be recommended as a useful summary of the clinical aspects of diabetes, but it should be possible to make several improvements for the second edition.

Handbook of Circulation

Analysis and compilation: PHILIP L. ATTMAN. Editors: DOROTHY S. DITTMER, RUDOLPH M. GREBE. National Academy of Sciences. Philadelphia and London: W. B. Saunders. 1959. Pp. 393. 52*s*. 6*d*.

HERE is tabulation in an extreme form. This book contains no text, only tables and a small number of diagrams with explanatory notes and lists of references. The tables contain an enormous amount of information about every conceivable aspect of the circulation in man and animals (including birds and fish), and even translocation in plants. Unfortunately, much of the material is unsuitable for tabular presentation, and generally the chief aim seems to have been to achieve comprehensiveness rather than the clear presentation of critically assessed information. The figures are often disappointing.

The list of contributors, containing 326 names, reads like a *Who's Who* of American cardiology, and also includes a few authorities of international renown from other countries. Such a large number may perhaps have been necessary to collect the huge volume of material, but the quality of the end-result suggests an overabundance of cooks. Nevertheless the volume has undoubted value as a source of references and as a quick means of discovering whether anybody has yet published measurements of almost any parameter of the circulation in plants, animals, or man.

Soil, Grass and Cancer

ANDRÉ VOISIN, membre de l'Académie d'Agriculture de France, chargé d'enseignement à l'École Nationale Vétérinaire d'Alfort (Paris). London: Crosby Lockwood. 1959. Pp. 302. 30*s*.

THE author of this book believes that the trace elements, particularly copper, and the mineral balance of the soil play a fundamental part in the welfare of animals and human beings. Few would dispute this, but most experienced agronomists and physiologists will feel that in this clever and well-documented book he has overplayed his hand. In spite of the 428 references to original papers and books, which imply a profound knowledge of the subject, he presents a picture which will strike some people as lacking just that balance which he appears to revere so much in Nature. The titles of his chapters tell their own story. Thus we are reminded that we are dust, that a disorder of copper metabolism is one of the causes of cancer, that there are milks which produce idiots, and that agronomic original sin is the principal cause of the mental illness of our children. This is strong medicine!

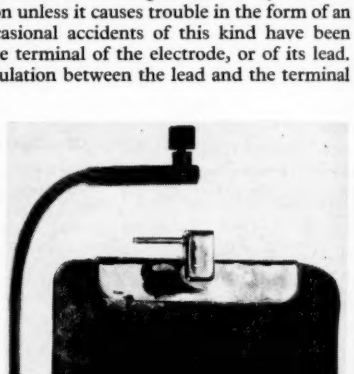
Experienced investigators, however, particularly those with wide interests, will find much to stimulate their minds in this book, and it will no doubt appeal strongly to those who believe that Nature, whoever she may be, is always right, and "man" is generally wrong! The book is not likely to find a ready sale among the medical profession, and it cannot be recommended for general reading without the proviso that, even if the author is not a "crank" (and we have the assurance of a scientist in the foreword that he is not), any disciple of his may very well turn into one.

Rheumatic Fever (*A Handbook for Parents*. London: Empire Rheumatism Council, Faraday House, 8–10, Charing Cross Road, London, W.C.2).—This six-page booklet is praiseworthy because of the importance it gives to prevention of recurrences of rheumatic fever and of subacute bacterial endocarditis by the wise use of penicillin. In places it has a somewhat old-fashioned air, which might make parents anxious while leaving some reasonable questions unanswered. It is free and obtainable (by doctors only) from the above address.

New Inventions

A SAFER DIATHERMY PLATE

THE indifferent electrode of the surgical diathermy machine receives little attention unless it causes trouble in the form of an electrical burn. Occasional accidents of this kind have been traced to faults in the terminal of the electrode, or of its lead. For example, the insulation between the lead and the terminal may wear and expose the underlying cable; the terminal itself may become detached from the plate and therefore transmit the whole of the current at a localised point; or the terminal may cause a deeper impression than the rest of the plate and thereby transmit a higher concentration of current.



To overcome these dangers and reduce the risk of a diathermy burn, the plate illustrated (see figure) has been in use at Southmead Hospital, Bristol, for the past two years. This plate has a male terminal, and the lead has a completely insulated female terminal. If the lead comes adrift from the plate, there is no exposed portion to transmit the current, since the whole lead (including the clamping screw) is covered by insulating material. The lead also has a double thickness of insulation from its terminal for a distance of about 18 in., the outer layer of which is transparent so that any fault at the junction of the lead and terminal can be seen easily.

I am indebted to the Endoscopic Instrument Company, of 62, Shirland Road, London, W.9, for help with the design and manufacture of this plate.

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Medical Needs of India

India has been standing on her own feet for twelve years; and in this short time her leaders have made a brave attempt to establish a Western-style democracy and bring her people into the garden of political maturity. As the only Asian country to try to do this, India has great opportunities; but both people and leaders are having to face realities from which they were long protected. " Independence " (the words " freedom " or " liberation " are not quite polite in India) has not removed or solved basic problems in the economic, social, or political spheres. Indeed, some of these have been exacerbated by recent developments, including the accelerated increase in population.

The medical profession is certainly to some extent responsible for this population pressure; but we have no need to be ashamed of that, provided that we help to cope with the consequences. At present the success of efforts to raise production is just about balanced by population increase, and the average standard of living remains appallingly low—how low can only be understood by those who have lived and worked in the country. It is perhaps unfortunate that so few British people have ever done this, except under the artificial conditions of war-time. One of the most depressing features of the world situation is that while the developed nations are becoming richer many of the others are still becoming relatively poorer. The people of the poor countries are well aware of this, but we in the rich ones are too often content to give thanks that we are not as other men.

For specifically medical problems, the Government of India has inherited a health service, including teaching hospitals and schools which were British-organised but have long been staffed almost entirely by Indians, mostly trained in India. Unfortunately, however, this great service was organised along semi-military lines: seniority within it determines status, and status is interpreted in a military sense. Even university chairs are included in the grades. There is a director of medical services in each State and a director-general at the centre, and their rule is no fiction: they can and do post senior people at pleasure, and determine in detail the staff of every hospital, school, or research institute. There is no open competition for appointments, and the methods of administration are rigid and old-fashioned. There are no local committees, medical or lay, to soften its rigours and spread a sense of responsibility. One would have expected this to have been changed after Independence, but it certainly has not. It is much to the credit of Indian doctors that their sense of duty to their patients is so strong, especially to the illiterate and semiarticulate who constitute the great mass. General practice is outside the service, and naturally many of the more intelligent young people enter private practice as soon as they can.

On the credit side there has been a big effort to train more doctors, especially by the opening of new schools. No attempt has been made to introduce grades with inferior training, and the standard of qualifying examinations is being maintained with a central pool of external examiners. This has meant abolishing certain of the State diplomas and closing some of the older substandard schools, some of which were run by Christian missionaries. Though some of the missionary hospitals and schools were outstandingly good and these continue—for example, Vellore, which has plenty of candidates for its medical school—the Government does not look with favour on missionary effort. On the other hand, there is political support for Ayurvedic medicine —a system which is based on the old four humours and employs cheap herbal remedies. The students of Ayurveda are not, as might be imagined, humble villagers any more, but smart young men in Western trousers with tucked-in shirts who carry stethoscopes and frequent well-built modern hospitals and colleges. There is much support for all this on nationalistic and religious grounds, even from distinguished " allopaths " themselves. On the other hand, there is little remaining prejudice against Western medicine, even among the more backward.

Postgraduate training is being expanded greatly, especially at new institutes which are attached to large specialist hospitals in the main centres and integrated with the local universities. This decentralisation allows more doctors to have instruction at less expense than in the vast central institute that was at one time proposed. (The whole scheme goes back to a committee formed in 1941 under the chairmanship of the late Sir BENNETT HANCE.) Many specialties are still undermanned by Western standards—e.g., anæsthesia and pathology. The new institutes are sensibly built to suit the climate of their locality: indeed, most are somewhat makeshift adaptations—frankly utilitarian and making no attempt to dazzle the foreign visitor. Entry to them is open only to members of the health service, arbitrarily chosen from above.

Not only has the supply of medical manpower to be considered, but also its distribution. This is extremely uneven, the larger centres being overdoctored while the backward countryside, where most of the real work is to be done, relies on such expedients as midwifery by the village barber's wife. There is nothing—apart from a sense of duty worthy of a saint—to attract doctors to the *mofusil*. Pay is execrable; no special facilities are granted for travelling or housing; no prospect is given for refresher courses or promotion; and professional and cultural isolation may be almost complete. Even in the cities pay is so poor that part-time private practice is

essential, while young practitioners are attracted abroad by better prospects. Moreover, a large proportion of Indian doctors still want to stay at home and live in the old way with all their relations under the same roof. To have a hobby is regarded as a serious eccentricity, and this applies especially to such things as field sports, gardening, or the study of natural history—to enjoy which some Europeans will endure, or even welcome, isolation.

The content of practice approaches nearer to the European now that purdah has virtually vanished (it was a Muslim importation) and the tropical diseases are within the range of eradication, though there is a great deal to be done with them yet. Rational nutrition is much limited by the sacredness of the cow; and the elementary rules of hygiene are disregarded. On the other hand, when malnutrition and epidemics become less overwhelming, conditions that used to be thought unusual in India grow more conspicuous—for example, rheumatic fever (even in the hot parts of the country) and especially tuberculosis. The importance of family planning is becoming appreciated and Hinduism raises no religious bar to this. As a corollary, child health is of growing interest to the younger parents.

Textbooks are relatively scarce. Indian printing and publishing are improving enormously in quality and quantity, but they have not yet caught up with the old-established British firms, and few Indian textbooks have been written. Fortunately English is still the common language of educated Indians, and they use British textbooks; but far more use of such works would be made if more of them could be brought within the means both of students and of teachers. Libraries are often good but cannot cater for the demand; nor can the few libraries of the British Council, which hold the only available copies of many important books, especially for postgraduates.

As for practical help, it is much less easy nowadays for European doctors to settle in India: even medical missionaries are being slowly eliminated as replacements fall due, fewer being allowed to enter than to leave. But active help for limited periods with specific projects is needed urgently, and under such schemes as the Colombo Plan this can often be given without prejudicing a career at home. The work can be deeply interesting and rewarding, and from all points of view it is a great pity that there should be difficulty in finding people to go. Lecture tours by the eminent, however acceptable, are no substitute for actual work in the country. At home, we can continue to welcome Indian doctors who come for postgraduate study, whether for specific courses or to work here temporarily, and must try to understand their difficulties when uprooted from their own social environment, especially coming from a land where family, social, and religious ties mean so much. There is sometimes a regrettable tendency to treat senior Indians as though they were juniors: they can teach much wherever they go, and more exchange professorships ought to be arranged for them. On the more commercial side, we could help to provide more textbooks and well-designed equipment. British manufacturers of sound drugs and equipment are not always well represented in India—in the face of competition from other countries which is not always as ethical as their own methods or products. None of this, however, is a substitute for personal visits in both directions, of a length sufficient to reveal helpful attitudes and common ground. Such visits can also show that our ways of control and administration are not as rigid as most Indians suppose.

India is a great country striving hard to advance despite an enormous burden of poverty, ignorance, prejudice, and indifference. Her doctors, in common with other professions, still look to Britain for guidance and with respect. We are losing a great opportunity if we do not respond.

Common-cold Viruses

AFTER 13 years of painstaking study at the Common Cold Research Unit it now seems likely that Dr. ANDREWES and his colleagues have succeeded in propagating—and what is more important, recognising in vitro—viruses derived from patients with colds. Prior to the work they describe in the opening pages of this issue, the only means of recognising common-cold viruses was their ability to induce colds in a proportion of human volunteers. Indeed one of the major achievements of the Salisbury workers has been the devising of techniques that enable meaningful experiments to be done with human volunteers.[1] Now, after many failures with orthodox conditions of tissue culture and with a variety of methods of detecting virus action, success seems to have been won.

Human volunteer experiments suggested that two agents (P.K. and H.G.P.) capable of causing colds were propagated in human embryo kidney cells maintained at 33°C in synthetic medium 199 [2]; so an intensive search for an in-vitro method of detecting virus was started. HITCHCOCK and TYRRELL (p. 237) showed that tissue cultures supposedly infected with Salisbury cold viruses interfered with the growth of a hæmagglutinating virus added 4 to 5 days later. Thus, when tissue cultures inoculated with cold virus were subsequently infected with Echo 11 or Sendai (parainfluenza) viruses, the yield of hæmagglutinin was significantly less than in control tubes of previously infected human embryo kidney cells. This enabled the simple in-vitro test to replace cumbersome human volunteer experiments for detecting virus. In this way it was found that the addition of glucose and bovine albumin to the 199 medium improved the propagation of the interfering agent. Using this technique, two agents were isolated from nasal washings of 4 patients examined. Virus was isolated from nasal washings in the acute but not the convalescent phase. Later, TYRRELL and PARSONS (p. 239) found that at least 3 strains (H.G.P., P.K., and S.E.B.) of virus isolated from common colds could cause cytopathic changes in human embryo kidney cells, and 2 of them (H.G.P. and P.K.) in monkey kidney cells as well. This observation

1. Andrewes, C. H. *New Engl. J. Med.* 1950, **242**, 235.
2. Morgan, J. F., Parker, R. C. *Proc. Soc. exp. Biol., N.Y.* 1950, **73**, 1.

sprang from an accident: trouble was experienced with toxicity in a batch of medium 199, so a new supply was secured; this happened to contain only 0·09% instead of 0·16% sodium bicarbonate, and cells in this medium showed a cytopathic effect when inoculated with H.G.P. virus. It seems that the low bicarbonate level was the all-important factor. Now, sparsely grown second-generation monkey kidney cultures grown in Hanks' solution, lactalbumin hydrolysate, and 2% calf serum with 0·03% sodium bicarbonate is the preferred culture system. Foci of degeneration appeared in 2 to 7 days and spread to involve the whole culture 5 to 10 days later. This is a technical advance of first-rate importance. As the Salisbury workers point out, their strains have not yet been conclusively shown to be common-cold viruses. But careful controls to exclude the possibility of picking up a stray virus were included at every stage, also the properties (size, ether resistance, pH, and heat sensitivity) of the agents recognised by volunteer experiments, interference, and cytopathic effect are very similar. The means now at hand both for tissue-culture study and human volunteer experiments should not leave this matter long in doubt. It will also be possible to determine whether the Salisbury viruses are all antigenically related to each other and what relationship they bear to other recently isolated viruses.

In the past decade well over 70 new viruses have been isolated from man, and many of them—notably the new members of the myxovirus (influenza), enterovirus, adenovirus, and reovirus groups—can cause severe and mild respiratory illnesses.[3–5] The symptoms of infection of the respiratory tract are relatively few, and, since one virus type can cause both severe and mild disease, many authorities, particularly in the United States,[6] believe that these new viruses probably account for a significant proportion of common colds. In view of their failure to isolate any of the new viruses—despite adequate technique—from their patients with colds, and also because they have failed to reproduce colds consistently in volunteers infected with these newer respiratory viruses, the Salisbury workers[4] have felt that the agent of common colds in adults as studied by them has yet to be identified. Moreover, they have inclined to the view[4] that the commonest variety of common cold in adults is a distinct entity caused by a distinct virus or group of related viruses. The clinical features of this sort of afebrile cold have been described by RODEN[7] and consisted mainly of increased nasal discharge.

HOPE SIMPSON'S careful inquiries[8] showed that many adults had as many as seven colds a year. He also noted that there are many features of the epidemiology of colds which are inexplicable by the theory of simple transmission, and he brought forward evidence suggesting that relative humidity was a very important factor. Thus, a low humidity favoured the development of the clinical manifestations of a cold—perhaps (though this is sheer speculation) in a way analogous to the influence of low bicarbonate levels in making manifest the cytopathic effect of the Salisbury virus on tissue culture. The demonstrated capacity of the Salisbury viruses to interfere with Sendai or Echo-11 viruses may perhaps mean that the Salisbury strains will themselves turn out to be susceptible to interferon—the recently described mediator of viro-interference which has many of the properties of a viral antibiotic.[9] Thus, it could conceivably be that these researches are pointing to both the cause and the cure of the common cold. But as our contributors declare, great caution is required in assessing their results at this preliminary stage. It has yet to be shown that these viruses cause colds, let alone all colds; and experience in virus diseases teaches that there is a very long delay between the discovery of the cause of a disease and the elaboration of adequate means for its control. The Salisbury workers are to be congratulated on taking a distinct step forward, and it is to be hoped that the pace of advance will now quicken against this tiresome and economically important malady.

B.C.G. Vaccination

THE second report to the Medical Research Council on B.C.G. and vole bacillus vaccines[10] should have removed any remaining doubts[11] about the ability of these vaccines to prevent tuberculosis in young people. Under the strictly controlled conditions of the trial the reduction in the incidence of tuberculosis over a five-year period that could be attributed to the vaccines was 83% for B.C.G. and 87% for vole vaccine. There seems no reason why similar reductions should not be obtained in this country when the vaccines are used under ordinary field conditions. The Ministry of Health authorised B.C.G. vaccination of 13-year-old schoolchildren in 1953; and SPRINGETT[12] has reported the effects of this scheme in Birmingham:

Vaccination of schoolchildren began in 1954, and all those reaching 14 years of age in or after March, 1955, should have been included in the scheme; so in 1958 all aged 14 and 15 had been eligible for tuberculin-testing and vaccination, together with almost all aged 16, a large proportion of the 17-year-olds, and a few of those aged 18, but none over that age. Each year, of some 15,000–17,000 children who left school, roughly three-quarters received their parents' consent to take part in the scheme, and over 85% of those tuberculin-tested were found negative and were vaccinated. In 1954, when vaccination began, there were 231 notifications of tuberculosis in Birmingham in persons aged 10–19 years; the corresponding figures for the next four years were 203, 154, 119, and 143. Children aged 14 were fully covered by the scheme from 1956 onwards; among them there were 19 notifications in 1955, 8 in 1956, and 6 in 1958. Those aged 15 were covered from 1957, and the number of notifications among them fell from 24 in 1955 to 3 in 1958. The reduction in the total notification-rates possibly attribut-

3. Huebner, R. J. Perspectives in Virology; p. 121. New York.
4. Andrewes, C. H. *Brit. med. Bull.* 1959, **15**, 225.
5. Sabin, A. B. *Science*, 1959, **130**, 1387.
6. Huebner, R. J., Rowe W. P., Chanock, R. M. *Ann. Rev. Microbiol.* 1958, **12**, 49.
7. Roden, A. T. *Proc. R. Soc. Med.* 1958, **51**, 271.
8. Hope Simpson, R. E. *ibid.* p. 267.
9. Isaacs, A., Burke, D. C. *Brit. med. Bull.* 1959, **15**, 185.
11. Medical Research Council Tuberculosis Vaccines Clinical Trials Committee. *Brit. med. J.* 1959, ii, 379.
12. Anderson, A. S., et al. *ibid.* 1959, i, 1423.
13. Springett, V. H. *Tubercle, Lond.* 1959, **40**, 432.

able to the B.C.G. vaccination scheme was estimated to have been 0·5–0·7 per 1000 per year.

The value of a B.C.G. scheme in a community depends on the proportion of individuals in it who are already infected at the age when vaccination is offered and the risk of infection after vaccination. In the M.R.C. trial (and in others) the incidence of tuberculosis in the observation period was highest in those who were tuberculin-positive on entry. This is, of course, not surprising; for tuberculin sensitivity in such circumstances indicates tuberculous disease, even though there are no other observable manifestations of it. But in assessing the benefits of vaccination, the spread of the lesions in this already infected group must be taken into account. It was estimated that, if all those tuberculin-negative on entry to the M.R.C. trial in 1950–52 at the age of 14 had been vaccinated, the reduction in tuberculosis among the whole group, both tuberculin-negative and tuberculin-positive, would have been 59% in the next five years. Since 1950, however, the risk of infection in this country had decreased. SUTHERLAND,[13] taking this decrease into account, has estimated the present scope for B.C.G. vaccination in England and Wales. Of the tuberculosis notifications in those aged 15–19 in 1958, he estimates that 52% could have been prevented if all who were tuberculin-negative at the age of 14 had then been vaccinated: the estimate for 1953 was 60%. While decline in exposure to infection continues, the scope for vaccination will also decline. B.C.G. vaccination of all uninfected who are now aged 14 would apparently reduce the incidence of tuberculosis in this age-group during the next five years by rather less than half. Although the decrease in the *proportion* of cases preventable has been slight in the past five years, the decline in the *numbers* has been great—from about 2950 among those aged 15–19 in 1953, to 1400 in 1958. A stage may fairly soon be reached where mass vaccination of older schoolchildren prevents only a few cases of tuberculosis in young adults, although vaccinations done in the past will, if protection is maintained, still be preventing tuberculosis in those over 20. SPRINGETT suggests that communities using B.C.G. vaccination in older schoolchildren should continue the procedure until notification-rates in the non-vaccinated groups are down to 0·1 per 1000 per year.

SUTHERLAND has also estimated the reduction in incidence of tuberculosis in those 15–19 years old which resulted from the local-authority vaccination schemes. In 1958, for example, the reduction was 241 notifications. But the number preventable if all children eligible had been vaccinated was about six times as large. Some uninfected children are not vaccinated because their parents do not consent. But the blame for the majority of the preventable disease in these young people rests not on the parents but on the local authorities, some of which either began the scheme late and developed it slowly or did not attempt it at all. In 1958 only 47% of all children aged 13 in England and Wales were tuberculin-tested and 37% vaccinated. If all had been tested the proportion vaccinated would have been about 79%; thus less than half the children who should be vaccinated were being vaccinated. It seems deplorable that the careful investigations of the Medical Research Council should not yet have convinced all local authorities that the children for whose health they are responsible can be protected from this serious disease, or that considerations other than medical ones should have prevented them carrying out the recommendations of the Ministry of Health. The Ministry, it appears, cannot force a local authority to use B.C.G. vaccine by the scheme they prescribe; yet at the same time they can prevent the vaccine being employed by local authorities in other schemes, even though the particular local circumstances warrant these. Thus, a child may be left unprotected either because the local authority will not provide vaccination within the authorised scheme, or because the Ministry will not approve vaccination out of the scheme.

The authorised scheme at present includes 13-year-old schoolchildren, and certain relatively small special categories at other ages.[14] Should the age of vaccination be reduced? Vaccination in the first few weeks of life could protect for an unknown period during infancy, and revaccination would be administratively easy in the early school years; but tuberculous infection of infants is declining rapidly, and it is unlikely that the great effort of attempting to vaccinate all infants throughout the country would be justified by the results. Moreover, the incidence of troublesome complications with the present intradermal route is higher in infants than in older children.[15] POLLOCK[16] discussed the advantage of reducing the age from 13 to 10. At this age fewer would already have been infected and more could be protected during the vulnerable years of adolescence. But, as he says,[17] " the tuberculin-positive proportion of the 13-year-old age group is diminishing each year . . . [and] the application of a mass vaccination scheme requires to be regularly reviewed as the epidemiological situation changes ". SUTHERLAND suggests that a central bureau be established in connection with the official vaccination scheme. In this way changes in the tuberculin-sensitivity of children in different parts of the country could be observed and interpreted, and the notified cases of tuberculosis at later ages related to previous tuberculin sensitivity and vaccination. Such a scheme has been working successfully in Denmark for several years.[18] This central collection of information has much to commend it; and if the eradication of tuberculosis, and not just its " control ", is the policy of the public-health authorities, it should not be administratively irksome. But its value would be reduced if the central authority did not have some power to compel local authorities to offer vaccination against tuberculosis. At the same time it might be profitable in planning national schemes to abandon the present rigid uniformity and to take into account major local differences in the risks of infection, even between parts of the same administrative unit.

13. Sutherland, I. *ibid.* p. 473.

14. Ministry of Health circular 7/59.
15. Gemmill, J. S. *Med. Offr*, 1959, **102**, 141.
16. Pollock, T. M. *Brit. med. J.* 1957, ii, 20.
17. Pollock, T. M. *Tubercle, Lond.* 1959, **40**, 399.
18. Groth-Petersen, E., Knudson, J., Wilbek, E. *Bull. Wld Hlth Org.* 1959, **21**, 5.

Annotations

RABBITS

BY the end of 1955 myxomatosis had destroyed over 90% of the rabbits in this country, but even as early as April of that year an attenuated strain of the virus caused extensive infection in Sherwood Forest. Since then the less lethal form of the disease has been recognised in most counties of England and Wales, and many people have assumed that this is the natural course of events and that the infection can only persist in the less severe form. In Australia Fenner [1] and his colleagues showed that the introduced lethal virus, which was different from our own, was soon replaced by less virulent strains and—which is more important—that after seven epizootics even the original virus killed only about a third of newly caught young wild rabbits. In Australia attenuation of the virus thus appears to have favoured the natural selection of genetically resistant rabbits, and myxomatosis can no longer be regarded as of great value in pest-control. So far as is known, no such selection has occurred here and British rabbits are no more resistant to the virus than they were before 1954.

Differences in the evolution of the disease depend among other things on the complex relationships between virus, host, and vector; and in Australia mosquitoes (which Fenner has likened to flying pins) are the principal vectors. Rabbits infected with less virulent virus will survive longer than those infected with a fully virulent strain: more mosquitoes will therefore have a more durable source of virus provided that the nodular type of lesion of the attenuated strains remains rich in virus. Under these circumstances natural selection will favour such strains, and indeed Fenner et al.[2] showed that even when the highly virulent European strain was introduced on a large scale into an already infected area it dominated the peak of the epizootic during the summer but was supplanted by the local attenuated strains within a year. Virus which is too attenuated may multiply so poorly that mosquito transmission is impossible, but such strains have not been isolated in the field.

In Britain outbreaks of attenuated myxoma infection are probably still increasing, but there is no sign that these strains are supplanting the original lethal agent. According to Andrewes et al.[3] evolutionary pressure here is more likely to favour fully virulent virus, partly, at least, because of the habits of the chief transmitter *Spilopsyllus cuniculi*, the rabbit flea. Fleas will leave a dead animal and spread the infection, but they may not leave it at all or only when there is little virus available to contaminate the proboscis if the animal survives or has a long illness. As Marshall and Fenner [4] point out this would, at least for a time, favour dissemination of fully virulent virus. It is a platitude that infectious agents which kill all their hosts end by committing suicide, and possibly our present situation, where fully virulent and attenuated strains exist side by side, is a temporary evolutionary compromise. How long it may continue no-one can predict; for much though Fenner and his colleagues have learned about the epidemiology of the Australian disease, we know much less here. How the virus persists between outbreaks, and why and how it suddenly reappears in some districts after months or years of absence, we still do not know. Possibly the discontinuity of the outbreaks in a population whose individuals have an average life-span of about a year will help to avert virus-resistance in rabbits. Even if we escape the Australian epidemiological dilemma, we obviously cannot now count on an enzootic disease such as myxomatosis since it is both unpredictable and uncontrollable as a method of reducing our rapidly increasing numbers of rabbits. There was severe damage to farm crops last year, and the activities of the rabbit clearance societies should be greatly increased and much more widely supported.

1. Fenner, F. *Brit. med. Bull.* 1959, **15**, 240.
2. Fenner, F., Poole, W. E., Marshall, I. D., Dyce, A L. *J. Hyg., Camb.* 1957, **55**, 192.
3. Andrewes, C. H., Thompson, H. V., Mansi, W. *Nature, Lond.* 1959, **184**, 1179.
4. Marshall, I. D., Fenner, F. *J. Hyg., Camb.* 1958, **56**, 288.

FLUORESCENT RED CELLS

IRRADIATED at a suitable wavelength, many substances of biochemical interest (porphyrins, stercobilin, certain vitamins, and chemotherapeutic agents, to name but a few) either fluoresce spontaneously or can be induced to do so by treatment with fluorescent material. Others do not readily combine with these dyes; and a few actively extinguish their fluorescence. That hæmoglobin belongs to this last category has been one reason why fluorescence microscopy has never attracted a following among hæmatologists. Kosenow [1] outlined the scope of the method in the study of white cells, platelets, and the immature members of the erythrocyte series; but he agreed with earlier observers that the appearance of hæmoglobin in the cell blots out all morphological and chemical detail.[2] Werth and others have shown that this transformation is due to active extinction by the hæm moiety of the hæmoglobin molecule.[3 4] Apart from occasional fluorocytes—cells which display brief red luminosity among the dark discs of ordinary red cells—the exceptions have been erythrocytes of patients with porphyria and lead poisoning.

A year ago Donáth and Lengyel,[5] of the Anatomical Institute of the University of Budapest, reported a series of experiments in which they had sought to overcome the fluorescence-extinguishing power of hæmoglobin without seriously damaging the red cells. Using various chemicals (such as sodium hypophosphate) they found it comparatively easy to impart fluorescence to the red-cell stroma and thus partly to overcome the blackout effect of hæmoglobin; but neither by introducing such substances nor by altering the ionic state of the hæm iron could they influence the behaviour of hæmoglobin itself. This they achieved, however, by treating red cells with hydrogen peroxide before staining or by applying the dye mixed with hydrogen peroxide: erythrocytes could then be made to fluoresce vividly both on smears and in wet preparations.

This work was taken up by investigators engaged in the study of possible variations in the hæmoglobin molecule in acquired disease. Martos and her colleagues [6] found that fixed minimal quantities of fluorescent dye were necessary to induce fluorescence in hæmolysates of given concentrations; and, more surprisingly, that this fixed minimal quantity changed in chronic illnesses. They now claim that such pathological states cause a structural change in hæmoglobin, and that this change can be detected by the altered capacity to extinguish fluorescence

1. Kosenow, W. Lebende Blutzellen im Fluoreszenz- und Phasenkontrast-mikroskop. Basle, 1956.
2. Wagner, K. *Wien. med. Wschr.* 1950, **100**, 808.
3. Werth, G. *Acta hæmat.* 1953, **10**, 209.
4. Werth, G., Eisenbrand, J. *Z. physiol. Chem.* 1955, **299**, 156.
5. Donáth, T., Lengyel, I. *Magyar orv. Hetilap*, 1958, **99**, 930.
6. Martos, K., Geszti, O., Lengyel, I. *ibid.* 1959, **100**, 973.

after hydrogen-peroxide treatment. Similar changes were noted after X-irradiation [7]: even after comparatively small doses, and before any other change in the blood-picture (such as lymphopenia), the blackout effect of hæmoglobin on the red cells became more resistant to attenuation by powerful oxidising agents.

These preliminary results still require a good deal of experimental support; and, once the experimental facts are established, they will have to be interpreted with caution. (The data available at present do not even exclude the possibility that haptoglobulins were partly responsible for the changes described.) Even at this early stage, however, the work reminds us that the genetically determined abnormalities of hæmoglobin are not necessarily the only ones; and that, impressive though the advances in hæmoglobin chemistry have been, important gaps still exist. When we ascribe hæmoglobinopathies to minute chemical flaws in the globin moiety of hæmoglobin and dismiss the hæm moiety as normal, we should reflect that many of the clinical features (such as those resulting from changes in the oxygen-binding capacity) clearly point to altered function if not to altered structure of hæm. Possibly in the experiments reported by the Hungarian workers the hydrogen peroxide led to chemical changes in the globin moiety of hæmoglobin which affected the fluorescence-extinguishing power of hæm. The phenomenon could then be analogous in some respects to the change in the congenital hæmoglobinopathies: it is certainly just as puzzling.

INFANTILE STRUCTURAL SCOLIOSIS

AT one time diagnosis in orthopædics was followed almost automatically by treatment, usually for some gross deformity which needed correction. Now, however, because orthopædic disorders are becoming less obvious and gross, knowledge of prognosis or the natural history of the condition is increasingly recognised as an essential preliminary to treatment. Many orthopædic conditions are essentially self-curing, and accordingly complicated or expensive or potentially dangerous treatments are contraindicated. Notable among such conditions are certain deformities of childhood in which time and growth are likely to correct the deformity—for example, most types of knock-knee and flat-feet, many deformities following fractures of the long bones, and even the gross deformities following an unreduced supracondylar fracture of the humerus.

In 1936 Harrenstein [8] described what is now known as infantile scoliosis—that is, scoliosis appearing in early infancy without obvious cause and, in particular, without gross congenital bony anomalies such as wedged vertebræ or fused ribs. In 1951 James [9] described 33 cases of infantile idiopathic scoliosis; and James et al.[10] have lately described the natural course of the condition in 212 infants first seen below the age of three years. In roughly a third (77) of these the scoliosis resolved spontaneously; in the remainder severe and progressive scoliosis developed. In the early stages no bony abnormalities were detectable on radiographic investigation; and in 1 child, who died at the age of eleven months, no abnormality could be discovered on either macroscopic or microscopic examination. It is still uncertain whether the resolving and progressive curves are basically the same at the beginning. If they are, discovery of the cause of resolution might lead to an important advance in our knowledge of the ætiology and treatment of idiopathic scoliosis. Meanwhile, there is much to be gained by further study of the natural history of severe deformities; and until this is understood it is wrong to claim that any particular treatment has been successful.

7. Geszti, O., Sztanyik, L., Lengyel, I., Martos, K. *ibid.* 1959, **100**, 975.
8. Harrenstein, R. J. *Rev. Orthopéd.* 1936, **23**, 289.
9. James, J. I. P. *J. Bone Jt Surg.* 1951, **33B**, 399.
10. James, J. I. P., Lloyd-Roberts, G. C., Pilcher, M. F. *ibid.* 1959, **41B**, 719.

SCHOOL PHOBIA

THE syndrome of " school phobia " was first described by Broadwin [1] in 1932, although the term was not coined until nine years later.[2] It consists in persistent refusal to attend school, the child remaining at home with the full knowledge of his parents. " Truants " behave differently, usually absenting themselves from both school and home. Hersov [3] has shown that these two groups differ: school refusers are more intelligent, of higher social class, work and behave better at school, are more timid, and have been less frequently separated from their mothers in early childhood. The mothers are often over-protective and there is more neurosis in the family. School phobics are afraid of separation from their mothers and homes; and Burns,[4] among others, has emphasised that it is this separation-anxiety rather than fear of school that is the underlying problem: they are not phobic in the accepted sense, and perhaps, as Davidson [5] has suggested, they would be better called mother-philes than school-phobes—a term which casts an undeserved slur upon the pedagogues. While school refusal is usually a symptom of a neurotic disturbance, truancy tends to be associated with delinquency.

The number of cases seen in clinics is undoubtedly increasing both in America [6] and in this country [7]; but Barber [8] has suggested that, in the Bristol area anyway, the increase reflects greater zeal on the part of school attendance officers, and the National Association for Mental Health after its two 1959 conferences on the subject said that it has no evidence of an overall rise.[9] It is very likely that many children now treated as neurotic were previously dealt with as truants, or regarded as having some uncertain organic condition; for in such cases children present characteristically with somatic complaints, especially abdominal pain and nausea on school mornings.

The treatment of early cases consists in firm support, and encouragement of mother and child towards a return to school. Attempts to force the child only generate greater panic. If this fails, psychotherapy, usually of both mother and child, may be required; but a compromise solution, such as allowing the mother to remain with the child at school, may bring about an early return. Change of school in itself is useless, for it is not there that the trouble lies; but such a change does provide a fresh start and, in combination with other methods, may help. Separation from the parents by residential schooling may be needed, but only after careful judgment and individual treatment; for in the obstinate case the child will immediately abscond. Half of Hersov's group of severe cases

1. Broadwin, I. T. *Amer. J. Orthopsychiat.* 1932, **2**, 253.
2. Johnson, A. M., Falstein, E. I., Szurek, S., Svendsen, M. *ibid.* 1941, **11**, 702.
3. Hersov, L. M.D. Thesis, Witwatersrand, 1957.
4. Burns, C. L. C. National Association for Mental Health: proceedings of the 15th inter-clinic conference; p. 26. London, 1959.
5. Davidson, S. Address to Association for Child Psychology and Psychiatry, Dec. 12, 1959.
6. Eisenberg, L. *Amer. J. Psychiat.* 1958, **114**, 712
7. Graham, J. J. *Times*, Nov. 23, 1959.
8. See *Lancet*, 1959, i, 564.
9. *Times*, Nov. 24, 1959.

required inpatient treatment; but on the whole the outlook is good, especially for children below 11 years old of whom 89% attending one clinic were going to school regularly [10]; over that age the figure dropped to 36%. The "hard core" cases were found to come from the most seriously disturbed families: in such cases the school refusal may well be a clinic refusal, and, later on, a work refusal.[11] Clearly, the sooner treatment is started the better; and this requires efficient and rapid communication between parents, school, and the many other agencies that may become involved.[12]

MEDIASTINAL MASSES

THE situation and radiographic appearance of mediastinal neoplasms, cysts, vascular abnormalities, and glandular enlargements sometimes give a clue to their nature, but short of thoracotomy an exact diagnosis is usually impossible. Lyons et al.,[13] reviewing a series of 782 mediastinal masses, urge that preliminary investigations additional to chest radiography should nevertheless not be neglected. They found that barium swallow and angiocardiography not infrequently helped to establish the diagnosis or to assess operability, and scalene-node biopsy [14] above all proved to be a most valuable ancillary procedure. Scalene-node biopsy established the diagnosis in 92% of lymphomas and in 72% of granulomatous lesions with otherwise negative findings, and was also the most fruitful line of investigation in metastatic mediastinal lesions. Lyons et al. emphasise that for full exploitation of the method technical experience is necessary: a point also made by Aikens,[15] who reports useful results with this procedure in various respiratory conditions—especially sarcoidosis and, to a lesser degree, bronchial carcinoma. In obscure mediastinal and pulmonary conditions it seems, therefore, that scalene-node biopsy may sometimes avert the necessity for thoracotomy.

EXPLORING SUBCORTICAL FUNCTION

WHEN medically intractable epilepsy is to be treated by local cerebral surgery, definition of the precise site where the epileptic discharge originates is important. Originally such operations were planned in relation to macroscopic abnormality of the cortex; but when the electrical substrate of epilepsy was recognised its location was assumed to indicate also the site of origin of the clinical seizure. On this basis brain tissue showing such activity, even if macroscopically normal, was sometimes removed. There is now increasing evidence that, although some relationship between the site of origin of electrical abnormality and epilepsy exists, the correlation is far from complete. The search for a spike focus, and the excision of regions where it arises, are therefore now less keenly pursued—though the results are often beneficial.

Earl Walker and his colleagues,[16] who have already contributed much to this subject, have reviewed the results of subcortical recording in temporal-lobe epilepsy. They note that the absence of surface activity, including that from sphenoidal leads, does not exclude a subcortical temporal focus. They also find that, as with surface activity, spontaneous subcortical spike discharges are often unaccompanied by any overt clinical attack: and they suggest that these non-ictal discharges seem not to affect the normal functioning of the area, so far as simple tests of mentation can show.

Stimulation of deep temporal-lobe structures and basal ganglia suggested that the threshold for excitation of amygdala and hippocampus is relatively low, and that spread of discharge from these areas is wide. Confusion and alteration of thought were common, as were visceral, vasomotor, and emotional changes. An interesting finding was that stimulation of amygdala, thalamus, and globus pallidus elicited pain in one half of the body. The general picture is of visceral and affective responses from a number of sites, including medial temporal, inferior frontal, and thalamic. But relatively few stimulations, even of those producing electrical after-discharge, gave rise to clinical features of any sort.

INFECTION AT THE HAIRDRESSER'S

MOST men choose their hairdresser for reasons of nearness, cheapness, or cleanliness. (Women add other criteria less easily summarised.) The "cleanliness" is judged, we would guess, by standards that are basically unconnected with health. People dislike the shop which is stuffy or which has a smell to which they are not accustomed. They do not care for a floor littered with shorn locks, or sheets which have not been laundered recently. With shame they may admit that they avoid the shop whose customers come from another income group (whereas they would share a seat on the omnibus without a thought). They seem to feel that they may "catch something". Yet the evidence that the hairdresser's shop plays any important part in the spread of disease is negligible. "Barber's rash" is primarily an eczema, often complicated by staphylococcal infection; and though it can be spread by the use of a common razor or towel, the bacteria more often come from the patient's own nose. Moreover, public shaving is a dying custom and many of those who have this disease have never been shaved. *Microsporon audouini* was certainly disseminated by the hairdresser, but ringworm due to this fungus is now rare compared with that derived from animals. (That it was commoner in boys than girls may have been due to the fact that small girls tended to have their hair cut at home and the close crop of the small boy allowed the fungus easier access to the skin.) Any ill-ventilated enclosure encourages the spread of respiratory infections, but the barber's shop cannot be more dangerous than the four-ale bar.

An attempt to give some objective value to the assessment of cleanliness in hairdressers' shops has been made in Glasgow.[1] Fifty establishments were subjected to thorough inspection and judged by much the same standards as those used for eating-houses, with particular attention to such things as the disinfection of instruments. As might be expected, there was wide variation between the shops: indeed, almost the only thing they had in common was poor sanitary facilities for the staff. Shops patronised entirely by women were on the whole cleaner than those reserved for men, but this is not surprising: in every walk of life men wear dirtier clothes and have dirtier habits. Many bacteriological examinations of premises and equipment were made; but the difficulty

10. Rodriguez, A., Rodriguez, M., Eisenberg, L. *Amer. J. Psychiat.* 1959, **116**, 540.
11. Warren, W. Cited by L. Hersov (footnote 3).
12. *Med. Offr*, 1959, **102**, 292.
13. Lyons, H. A., Calvy, G. L., Sammons, B. P. *Ann. intern. Med.* 1959, **51**, 897.
14. Daniels, A. C. *Dis. Chest*, 1949, **16**, 360.
15. Aikens, R. L. *Canad. med. Ass. J.* 1959, **81**, 891.
16. Lichtenstein, R. S., Marshal, C., Walker, A. E. *A.M.A. Arch. Neurol.* 1959, **1**, 288.

1. Wilson, T. S., Carter, H. S. *Med. Offr*, 1959, **102**, 249.

here is that, to be really useful, numerical values must be compared with other numerical values, and one would like to know how the microflora of the hairdresser's shop compares with that of the railway carriage or the doctor's waiting-room. The failure to recover ringworm fungi was interesting and encouraging but likewise evokes a further question: how common was the disease in Glasgow at the time?

Fastidiousness is generally an aid to hygiene, and people who normally prefer to keep to their own brushes and towels are entitled to demand a high standard of cleanliness in places where such things serve a succession of customers. They will therefore welcome the medical attention to these matters which this investigation shows. Nevertheless the general notion that hair is rather dirty stuff is now largely irrational, dating perhaps from the days when it nearly always *was* rather dirty. On bacteriological examination, clean hair shows few bacteria in it and even fewer that are likely to cause disease.

TEAMWORK FOR CLEFT PALATES

THE management of babies with cleft palate has rightly become the concern of a team rather than an individual. This enlightened approach, which has been particularly evident in Britain, was demonstrated during the L.D.S. centenary celebrations last July by the choice of subject for the main scientific symposium—namely, Treatment of the Cleft Palate.[1] An embryologist, a plastic surgeon, an orthodontist, and an expert in prosthetics outlined an integrated attack in which none could succeed alone. No claims for any startling technical advance were made, though some discussion centred on the scope of the early "orthopædic" treatment advocated five years ago by McNeil.[2] On this issue one point is clear: that no intraoral appliance in early infancy (or later) can conceivably achieve closure of the soft palate—and therefore the operative repair of this vital structure cannot be obviated. It was emphasised that patients must be considered as people—"this lesion is a fissure in the palate completely surrounded by a human being". It was imperative that they should not be allowed to reach adult life as vocal, cosmetic, or dental cripples.

The surgeon should at the first opportunity give the parents, who may be appalled by their child's deformity, an honest but reassuring outline of the therapeutic plan. Two-thirds of palatal clefts are "complete", involving lip and alveolus; and the stages in these severe cases can broadly be summarised as follows: repair of the lip and nasal floor is carried out at 3 months, and repair of the hard and soft palate at 18–24 months; orthodontic supervision (which should be begun soon after birth) can reach the stage of maxillary expansion at 4–6 years; speech therapy (if indicated) should also be begun at about this age, but in a good home this task may be supererogatory. Prosthetic treatment often consists in merely replacing an absent lateral incisor; but a few surgical disasters are still seen, and for these (as for the rare cases where primary surgery is impossible) an obturator may sometimes prove startlingly effective in providing clear speech. Finally, secondary surgical adjustments to lip, septum, and nose may be indicated and are usually deferred until the patient is 15 or older.

At the symposium an issue of particular importance was raised—the operative mortality and its possible relation to the patient's age. Strong claims have been made that the palate should be repaired at the first birthday, and in a recently published series[3] the subsequent operative mortality was 3·7%. This is at striking variance with the figure given by Fogh Andersen (cited in the same paper), who operated at about the 2nd birthday with a death-rate of 0·6%. This comparison offers up-to-date evidence for the view, held in earlier days, that a young baby is not as a rule an acceptable risk for this major procedure. While the hazards have been enormously reduced, particularly by modern standards of anæsthesia and general management, they have not yet been eliminated. In the opinion of many experienced surgeons sound reasons still exist for deferring operation until the deciduous dentition is complete—and there may be special considerations which justify postponing operation for 3 or 4 years. Contrary arguments, based on theories of the developing patterns of speech, carry little weight when set against the cost in lives. Perfect speech is an admirable goal; but the death of a child once in every thirty operations is a heavy price. As the published results of Fraser and McCredie,[4] Davies and Danks,[5] and others have shown, the death-rate ought not to exceed 0·5%—and "should be nil".

DIAGNOSIS OF MULTIPLE PREGNANCIES

AN interesting report on the use of the electroencephalogram in the diagnosis of multiple pregnancy by identification of fœtal cardiac activity has appeared in the United States. Using a standard eight-channel Grass model III electroencephalograph, Novotny et al.[6] studied 321 tracings from 295 patients. They found that the 28th to 36th week of pregnancy was the most difficult time for demonstrating fœtal heart activity, the best results being obtained between the 20th and the 28th week. In 81% of cases single or multiple pregnancy was correctly diagnosed, or fœtal death confirmed; and in the 20th to 28th weeks the proportion was 90%. Difficulties were encountered as a result of excessive maternal muscle artefact, excessive fœtal activity, poor cooperation by the patient, failure to empty the bladder, or maternal tachycardia. Accordingly 20 tracings were technically unsatisfactory for interpretation, while in 38 others either the fœtal heart activity was not demonstrated although the fœtus was alive or only one heart was revealed when two or more fœtuses were present.

As an alternative to the positive demonstration of multiple pregnancy by X-rays, this method cannot yet be accepted completely. Because of the dangers to the undiagnosed second twin during delivery, the method of diagnosis should be thoroughly reliable; and the likelihood of error with the electroencephalographic method is not outweighed by the very early diagnosis which may be possible (twins were correctly diagnosed at 16 weeks and triplets at 20 weeks, while an X-ray at 24 weeks in the same case of triplets was still inconclusive). The great advantage of this method lies in the avoidance of radiation hazards; and if further experience were to increase its accuracy it might prove a valuable additional means of investigation.

Sir JAMES PATERSON ROSS is to succeed Sir Francis Fraser as director of the British Postgraduate Medical Federation when he retires on Oct. 1.

1. *Ann. R. Coll. Surg. Engl.* 1959, **25**, 225.
2. McNeil, C. K. Oral and Facial Deformity. London, 1954.
3. Reidy, J. P. *Brit. J. plast. Surg.* 1959, **12**, 215.
4. Fraser, I., McCredie, J. A. *Brit. med. J.* 1955, ii, 867.
5. Davies, R. M., Danks, S. *Anæsthesia*, 1953, **8**, 275. See *Lancet*, 1959, i, 239.
6. Novotny, C. A., Hass, W. K., Callaghan, D. A. *J. Amer. med. Ass.* 1959, **171**, 880.

Special Articles

THE MARRIED MENTAL DEFECTIVE
A FOLLOW-UP STUDY

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SHEFFIELD

EVEN before the Royal Commission's report, public opinion was fast moving away from the ideas current at the beginning of this century when mental-deficiency legislation was being formulated. Though prohibition of marriage was dropped from the original Bill, under the Mental Deficiency Act of 1913 many mental defectives were segregated in colonies for the years when they were most likely to bear children. As recently as 1949 the Ministry of Health expressed the opinion that mental defectives were generally unfit for the responsibility of marriage and of parenthood, and that, even if they were able to conform to normal social requirements in sheltered conditions in the community, they were rarely able to stand the strain of bringing up children and managing a household.

Today some well-informed people are undoubtedly seriously disturbed by the possible social and genetic consequences of community care. Detailed studies of intelligence levels among the children of mental defectives are conflicting (Penrose 1938, Brandon 1957). Little attention has been paid to the social performance of families in the community, though several follow-up inquiries (Ainsworth et al. 1945, Mickelson 1947, Hartzler 1953, Wolfson 1956) throw some light on the American scene. The object of the present investigation was to choose a random sample of the married defectives in Sheffield and follow them up systematically to see what success they had made of marriage.

METHOD

We selected the cases by going through the departmental records of all mental defectives ascertained since 1915. Of the 2877 records scrutinised 640 referred to patients in mental-deficiency hospitals, and 1293 to mental defectives under statutory supervision. The remaining 944 had been discharged from statutory supervision. Defectives are usually discharged from statutory supervision when they have shown themselves capable of leading a stable life within the community.

Marriages listed for investigation were those recorded on the case-notes. These numbered 120 men and 122 women including ten instances in which ascertained defectives had married each other. Other marriages may have occurred after discharge from supervision, but we investigated only those given in the case-notes.

THE SPOUSES

Of the original 242 defectives 45 (19%) are untraced. 19 of those untraced are known to have moved from Sheffield, though some may have returned unknown to the department. No attempt was made to follow up any patient outside the city boundary, because there is a danger of rediscovering the less satisfactory families and overlooking those who have merged successfully in the community. Searching for families through intermediary authorities adds a further element of uncertainty as to whether the people traced are representative of those originally selected. Eventually 197 (81%) people were traced. Of these 98 were still under statutory supervision (including 13 in institutions) while 99 had been discharged. An inquiry was made and a pro-forma completed by the district health visitor or mental welfare officer on the basis of an interview or from previous knowledge. Opinions have occasionally been modified in the light of further information from other departments or from voluntary bodies.

Intelligence level

The intelligence quotient of 122 of the defectives in the survey was recorded. In 93 (76%) the I.Q. distribution lay between fifty and sixty-nine; 13 (11%) were above this range and 16 (13%) below. There were proportionately more men with I.Q.s over sixty-five, probably because they were ascertained as mental defectives on account of behaviour difficulties at school or other indiscretions, despite a moderate level of intelligence.

Size of Family

The mean age of marriage among the men was 22·2 years compared with 25·2 years among the women defectives. In the country as a whole men marry 3 years later than women. Live births, however, were 50% greater than the norm for women married at the same age and for the same length of time. The birth-rate was also appreciably above that in families of unskilled workers (Registrar General 1959).

Infant Mortality

Information about infant deaths was often incomplete and infant mortality has only been assessed since July, 1944. Nevertheless 26 infants are known to have died, equivalent to an infant-mortality rate of about 73 per 1000 live births. This is in line with earlier findings (Departmental Committee on Sterilisation 1934, Juda 1934).

Employment

Of the mentally defective husbands 34 were in unskilled occupations but 24 were doing semiskilled or possibly even skilled work. There was not enough information to classify the employment of 13. 5 husbands were temporarily unemployed, 13 were chronically unemployed, 6 were in mental-deficiency hospitals, and 5 were in prison (i.e., 29% were not in employment). Of the mentally defective wives only 14 were employed outside the home.

9 of the men were registered as disabled persons, and of these 4 were unemployed. 2 others, who were among the chronically unemployed, were on the blind register.

Criminal Record

5 husbands were serving a prison sentence and a further 7 had served previous terms of imprisonment. The offences included robbery with violence (1), larceny (4), child neglect (2). Another 30 had been before the courts for stealing, sexual offences, or minor misdemeanours. 11 of the mentally defective wives had appeared before the courts for offences such as prostitution and theft but only 1 had served a prison sentence.

Broken Marriages

38 divorces or permanent separations were met in the survey, equivalent to 20% of the total families traced. 9 marriages were obviously unsatisfactory even to the outsider. Nevertheless most of the marriages seemed to be reasonably happy and stable even when the families presented problems to others.

Child Care

34 families were known to the National Society for the Prevention of Cruelty to Children; and the children's department had been concerned with a further 11 families over reports of neglect or other circumstances that led to the children being placed in the care of the local authority for several months or longer. These 45 families were almost a third of the families who had one or more children—a disturbingly high proportion. According to departmental records the childhood background of the defective parent was considered unsatisfactory in 28 of 41 neglected families (68%) compared with 56 of the remaining 126 families (44%).

THE SECOND GENERATION

Of the 377 children 46 were unsuitable for education in an ordinary school, or were so retarded that it was unlikely that they would prove suitable. This is equivalent to 10·6% of live births or 12·2% of children surviving the first year of life.

6 children were in mental-deficiency hospitals, 26 were in special (E.S.N.) schools, 9 were at occupation centres, 5 were retarded children under school-age. We saw all the pre-school children personally and carried out an intelligence test where possible.

Many head teachers are very tolerant of backward children and it seemed that there might be other retarded children from the survey families whose names were not put forward for transfer to a special school. Evidence is available from the results of routine group intelligence tests given at ordinary schools as part of the secondary selection procedure. Records were traced of 57 (76%) of these children in the survey families. 59% of the test scores fell between eighty and one hundred; 12% were above this range and 29% below. Only 3 children had scored under seventy in both of two I.Q. tests, which suggests that few mentally retarded children had been overlooked.

Among the survey group 11·6% of schoolchildren were attending special (E.S.N.) schools; this percentage is about 17 times higher than for the Sheffield school population as a whole. The proportion of children of compulsory school-age who had been reported as ineducable (5·6%) was also 17 times higher. Of the 23 survey children attending a special school for the educationally subnormal, only 2 had an I.Q. above seventy (Terman-Merrill).

SUCCESSFUL AND LESS SUCCESSFUL

26 families could be described as problem families in the sense that they had presented problems to several departments of the corporation and to other social agencies. The home environment seriously jeopardised the mental and physical development of the children. In 15 (58%) one or more children had to be removed from the care of the parents, though the family was not necessarily split up at the time of the survey. Several other families undoubtedly would have fallen into the category of " problem family " but for the fact that at the time of the survey the parents had separated and the family had ceased to exist as an entity. Of 10 families where both man and wife had been ascertained defectives 5 were regarded as problem families: of the other 5 marriages only 2 could be considered satisfactory, 1 of these being a childless couple.

40 families out of 90 (44%) where the man was defective and 38 families out of 87 (44%) where the woman was defective seemed to be living reasonably happy and normal lives. They were self-supporting within the community and not a special problem to any social service. Many families in the survey showed unsatisfactory features such as poor child care, slovenliness, or obvious signs of marital disharmony. Sheridan (1956) has observed that temperamentally stable mentally defective mothers can cope with their households fairly well while they have only one or two children, but when their family responsibilities outgrow their capacity they become overwhelmed. Our own experience supports this view. Excluding the 38 marriages where the husband and wife had separated, there were 92 marriages childless or with one or two children, and 57 marriages with three children or more. Of the small families 59 (64%) appeared to be quite successful from the point of view of social adaptation, whereas among the larger families only 22 (39%) were satisfactory. Of the 15 families where husband or wife had an I.Q. of under fifty only 2 were in the satisfactory group, and there was reason to doubt the validity of their I.Q. assessment.

Discussion

The picture that emerges is not clear-cut. Young people of low ability are destined either for success or failure; and, if only there were some sure method of differentiation, it would be easy for the community to arrange for a psychiatric assessment and help them in a rational manner. In fact, however, this is far from possible. Some of those with the most depressing record suddenly achieve stability, and settle down in a way that is a credit to them. With I.Q.s of fifty or above there seems no close correlation between intelligence level and social adaptability, though we doubt whether a mother with an I.Q. of under fifty-five or so is really mentally capable of raising a family satisfactorily. Even here, however, where there is only one, or possibly two, children, the standard of care may be adequate. The impression of the visitors was that mental defectives tend to choose, or be chosen by, a partner of about their own intelligence level. Undoubtedly, however, that little extra ability, if it is there, can make all the difference in enabling a family to manage its affairs in a way acceptable to the community.

Though families exist where all members are obviously mentally subnormal, usually they tend to show ranges of ability not so very different from the average. The size of the families is larger than the average, though the additional births are to some extent balanced by the number of infant deaths. The employment record of the defectives was fairly good, despite a hard core who contributed little or nothing to the support of themselves or their families. The proportion of men who had fallen foul of the police was rather high. Most had been dealt with under the normal penal procedure, though 13 appear to have been admitted to an institution as a direct result of the offence. In the survey a fairly high proportion of the children found neglected were the offspring of defective parents who themselves had an unsatisfactory upbringing.

The reasons why some families have failed may appear only too clear, but an explanation of the successes must take account of social adaptability and tolerance. Similarly, the community must be tolerant and adaptable. However comprehensive the mental health services, there will always be those who do not conform to recognised codes of behaviour. Patience and forbearance will be necessary if the mentally handicapped are to live within the community in peaceful coexistence.

This follow-up study could not have been carried out without the health visitors and mental welfare officers who undertook the field work. Much confidential information has been provided by social agencies and by other departments of the local authority, but the opinions expressed are our own and do not necessarily reflect the views of the agencies consulted or the Sheffield City Council.

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THE AMERICAN SCENE

SOME striking facts about medical developments in the United States are given by Dr. WILLARD C. RAPPLEYE in his report on Dec. 1 as president of the Josiah Macy, Jr., Foundation.[1]

Support for Research

He begins by speaking of the "enormous expansion of research funds now available from governmental and other sources". For the National Institutes of Health at Bethesda, the U.S. Congress voted about 400 million dollars, or nearly 50 million dollars more than the institutes asked for. In authorising this increase of 36% over the previous year's expenditure President Eisenhower expressed concern lest it should actually "lower the quality of the projects supported", divert into research too much of the man-power and other resources needed for "equally vital teaching and medical practice", or make medical research and training more dependent on federal funds. But large sums are at present collected by voluntary agencies: for example, last year the American Cancer Society raised nearly 30 million dollars, the National Tuberculosis Association nearly 26 million, the American Heart Association over 22 million. With smaller incomes, the Muscular Dystrophy Association raised nearly $5^1/_2$ million dollars, the National Association for Mental Health 5 million, and the Arthritis and Rheumatism Foundation 3 million.

Dr. Rappleye refers to the way in which the control, direction, and utilisation of research-workers is being detached from the educational institutions, so that many investigators are becoming "journeymen scientists", often with little or no responsibility for teaching or institutional services.

"Comments are increasing regarding the large numbers of young scientists who are employed on short term research or traineeship funds whose future livelihoods and careers are uncertain. Hundreds of these young men and women are becoming worried about their futures which is being reflected in reluctance of others to enter the field so largely dependent on governmental, foundation, industrial or other impermanent funds."

Medical Education

The amount of money spent on medical education represents only 1% of the total expenditure for health services (and it includes numerous hospital services which should partly be supported from non-educational sources).

"One fortieth of one per cent of corporate profits of American industry before taxes would be sufficient to cover the teaching deficits of the 85 medical schools. Private practice and medical insurance fees are helping in a number of instances to maintain the clinical staff. More financial support from various sources is urgently needed if the obligations of medical education as the essential feature of an adequate health service of the nation are to be maintained."

Though usually the university is regarded as responsible for the preparation of doctors, a substantial part of the clinical education of medical students is often provided in non-university hospitals. Moreover, over three-quarters of the 12,469 approved internships and over half the 31,818 residencies are in such hospitals.

"Fortunately, many of the non-university hospitals now have modern laboratory and other facilities and professional staffs of excellence and good training, some of them on a full-time basis, who would be able to give a high quality of instruction to medical students, to house staffs and local practicing physicians if given the opportunity and incentive. A large reservoir of potential training opportunities exists which might be utilized through proper educational leadership and guidance."

"In view of the avalanche of new knowledge and the masking of scientific developments in part behind commercial exploitation the problems of keeping a physician in practice up-to-date presents a major challenge to the profession, hospitals and medical schools". New and vigorous plans for postgraduate education must be made if the public are to get the benefit of scientific advances. This Dr. Rappleye describes as a "crucial aspect of modern medical care". Writing of the possible incentives to practitioners to continue their education, he says that "the idea of a periodic re-examination of physicians is again under review".

Meanwhile there is the still growing problem of absorbing graduates of foreign medical schools: last year there were 9254 foreign-trained interns and residents in 821 hospitals.

A quarter of these were in New York, where "in the municipal hospital system eleven of the institutions have not a single graduate of an American school." Most of the foreign group in New York City come from the Philippines (1598), Turkey (587), and Mexico (500). There are now about 2200 Americans studying medicine abroad—usually because they cannot get into an American school. Yet "some of our own institutions have not enough acceptable applicants to fill their classes, sometimes because of geographical restrictions on students in certain state medical schools."

The Surgeon General's Consultant Group on Medical Education has recommended an increase in the annual output of American medical schools by 3600 (at present it is about 6800), and has proposed the creation of 20–24 new schools.

Prepayment for Illness

Discussing the continuing difficulties of the Blue Cross and Blue Shield schemes under which so many Americans insure against illness, Dr. Rappleye says:

"The challenge immediately ahead is the extent to which premiums on a voluntary basis can meet the costs of expanding hospital services. There is some evidence to indicate that the premium income on a voluntary basis is not likely to rise much above one-third of the total costs of hospital care in the aggregate. That this figure may be somewhere near correct is illustrated by the recent decision of Canada to provide complete hospital service for the entire population on the basis of a $33^1/_3$ per cent contribution from the individual through pay-roll deductions or other devices. It is of interest that Austria has just adopted the same formula."

Proposals have recently been made by the labour unions of New York to organise their own chain of hospitals and medical services, and the New York County Medical Society has offered to cooperate in such a plan. In Detroit a Community Health Association, sponsored by the United Automobile Workers Union, will shortly be launched. The American Federation of Labour/Congress of Industrial Organisations are now in favour of grants to medical and dental schools not only for equipment and plant but in defraying operating costs. "They continue to recommend the pre-payment plans for consumer-controlled health service plans.

"Younging" of the Population

A new set of problems, Dr. Rappleye says, is confronting the country and medical services through the "younging" as distinguished from the "ageing" of the population. The number of people under 20 years of age will reach 90 million, or 40% of the population, by 1970.

"An interesting prediction is that by 1970 those of 65 years of age or older (roughly 21,000,000) and those below 20 years

1. The Foundation's address is 16, West 36th Street, New York 36.

of age (roughly 90,000,000) will represent over 50 per cent of the entire population of the country. It is obvious that those between the ages of 20 and 65 will be bearing over one-half the economic and certain other responsibilities of the nation."

Medicine and the Law

Delusions or Cruelty?

A HUSBAND petitioned for divorce on the ground of his wife's cruelty. The essence of his case was that from 1954 onwards the wife persistently made false and baseless accusations against him that he was carrying on with other women, and had nagged him on this theme incessantly, for hours at a time.

Early in 1955 the wife, who was then about 35 years of age, was seen by Dr. J. G. Hamilton, consultant psychiatrist at the Bethlem Royal Hospital. On March 12, 1955, the wife was admitted to that hospital, and remained there until May 28, 1955. She then returned to live with the husband. She soon renewed her accusations, suggesting that her husband had been carrying on with other women while she was in hospital. In October, 1955, she was again seen by Dr. Hamilton. She then admitted that some of her accusations against her husband were false, and that she knew they were false when she made them. She said that some of the things she had said to her husband had been said in order to trick him.

Dr. Hamilton gave evidence that, in his opinion, the wife was paranoic, and suffered from delusions; she was never certified and he thought it was improbable that she was ever certifiable. He said that she sincerely believed that her husband had affairs with other women, and, despite the fact that she had admitted that some of her accusations were untrue—which was exceptional in such cases—he did not consider that that was enough to outweigh the other reasons for saying that she was deluded. When she made these accusations against her husband, she knew the nature and quality of her acts, in that she knew she was accusing her husband of unfaithfulness, but she did not know that what she did was wrong. Indeed, she believed that what she did was right. She felt that she was a wronged person who had a great grievance and that it was proper for her, believing that her husband was being unfaithful to her, to say so and to act as she did. The wife crosspetitioned on the ground of cruelty.

Mr. Justice PHILLIMORE said that with regard to the husband's charge of cruelty and the answer which had been put forward, there was a presumption that a person was sane so as to be legally responsible for his or her acts. The burden of proof was on the wife to prove that, by reason of her state of mind, she either did not know what she was doing or did not know that she was doing what was wrong. If she discharged that burden of proof, she could not be held guilty of cruelty. It was quite possible that in the autumn of 1954 and, indeed, until her discharge from hospital in May, 1955, she did not know that in making these charges against her husband she was doing what was wrong. When, however, she recanted, and admitted that she knew that some of her accusations were false and that some of the things she had said had been said with the object of tricking her husband, it was impossible to hold that thereafter she was not legally responsible for her conduct. Her continued accusations therefore amounted to legal cruelty. The husband was accordingly granted a decree *nisi*. As the wife had also made out her crosscharge of cruelty against the husband, she, too, was granted a decree *nisi*.

Pethers *v.* Pethers & Wolff—*Probate, Divorce, & Admiralty Division:* Phillimore, *J.* Jan. 18, 1960. Counsel and solicitors: Miss M. Morgan Gibbon and Trevor Guest (Copley, Singleton & Billson); Dudley Collard (Jaques & Co.); Leonard Pearl (Walford & Co.).

D. R. ELLISON
Barrister-at-Law.

In England Now

A Running Commentary by Peripatetic Correspondents

I BELIEVE I have at last found a valid use for the drug-firm circulars on antibiotics. To make my point I must describe a scene which is continuously repeated throughout the country.

Seven of us are seated in the board-room of the Peripheral Regional Hospital Board to select the best candidate for the post of consultant omphalologist to the Central Group of Hospitals. We have seen six excellent candidates, all with the correct qualifications (M.D., M.R.C.P., F.F.O.), each at an appropriate stage in his career. Dr. F. has been eliminated at the first round because he made an ass of himself at interview: he had not only failed to visit the hospitals, he was also completely unaware that the professor on the committee had written a monograph on omphalomancy.

The chairman now goes round the table for the second time, asking for two names, please, in order of preference. It is immediately clear that we are going to have a long session, for there are three first votes for Dr. A. and three for Dr. B. This, mind you, is hardly surprising. Dr. A.—the local boy, no genius but a sound chap—has collected the first votes of the three local members: Dr. B.—the bright boy from the metropolis, with strings of publications and eulogistic references from Harley Street—has the votes of the three others. The Chairman has not revealed his hand. The pro-A faction ("We cannot be sure that this man B. would fit in with local conditions") is adamant, and the pro-B. element ("Our job, Mr. Chairman, is to appoint the best man") is equally immovable. The argument is becoming heated: it looks like an impasse.

It is suddenly noticed, however, that all six second votes have gone to Dr. C., who is neither metropolitan nor local, who has spent half his time in teaching hospitals and half in regional hospitals, who has a wife and two children, who has written just three articles, and who has a pleasant personality. "I liked that man," says the Chairman, "I thought he interviewed well." The factions dissolve, all agree to support Dr. C. He is brought in and, somewhat to his surprise, offered the job. In point of fact—and less surprisingly—he will do it very well.

The moral? Clearly, Dr. C. has shown "broad-spectrum acceptability". Dr. A. and Dr. B. should have spent more time over breakfast, reading the literature instead of just sorting out the blotters.

* * *

Unlike another peripatetic correspondent, I have never felt so close to my dustmen as all that. Indeed, it wasn't until it cropped up in the public-health course that I realised how this particular face (of Britain, I mean, not the dustman) was changing. Now not only have our City Fathers equipped themselves with end-loading gravity-packers, but so have the R.D.C. down the road. But, however much they may enchant the kids (and me) by sticking their tails up in the air, I still can't see how they're emptied. Do they stand on their heads or their tails, or are the contents so densely packed that some unfortunate dustman—perhaps dignified by the status of "disimpactor"—has to dig it all out with a shovel?

* * *

In Service medicine you meet some interesting symptom-complexes in the different age-groups.

The *under-twenties*, with a string of symptoms, any two of which are incompatible with life, linked with rosy cheeks, a horse-like appetite, football twice a week, and dancing every third night till 3 A.M., present the unusual combination of desperate illness in a healthy body. Unaccustomed to sickness the mild symptoms of a cold are resented as a gross departure from normal. The giddiness induced by a slight pyrexia is regarded as impending dissolution and the dysphagia of swollen tonsils as acute diphtheria or worse. This age-group is highly suspicious of older men (of from 21 up), and you must view their symptoms in the same grave light as they do.

The *twenties to twenty-fives* form an interesting subgroup. The main morbidity here is love, Yogi, surrealism, and a desire to get away from it all. The mortality is nil and they improve amazingly in the warmer summer weather. Consultations in this group are somewhat one-sided as the patient does most of the talking.

The *twenty-fives to thirties* are connoisseurs of trivia. The slight distemper in the temple following guest night is not looked on as divine retribution, but as an early sign of brain tumour which should be investigated at Queen Square at once. The slight metatarsal ache following the tango, " but never the foxtrot doctor ", is expected to bring a posse of leading London orthopods at a sharp trot.

For those from *thirty upwards* any form of sickness is out of the question. The subject with a wife, children, a house, insurance, and a car (none of which he can afford) is only concerned with the struggle for survival. Surgery must, as it were, be done on the run, and he is only brought to his knees by some catastrophe like mesenteric gangrene.

* * *

Since I left the National Health Service and joined the medical department of a large pharmaceutical organisation, I have had many opportunities to compare and contrast these two ways of life.

For a start, it is a great relief to find that I am no longer part of the registrar problem, and I hope that the world of commerce will prove less uncertain for me than the clinical rat race.

The material benefits are obvious. The work is light and most remunerative. Until the past few months I had not had regular Saturday mornings off since I went to kindergarten at the age of five, and to have every Saturday morning to myself is indescribable luxury. I no longer find that medical emergencies clash with social engagements, though, perhaps surprisingly, my plans still often have to be altered; for the business executive always changes all his arrangements at least once, at the last moment.

It is a pleasure to eat and drink in the style to which one would like to be accustomed, and memories of dreary and monotonous hospital food are soon forgotten as one becomes used to excellent and leisurely meals eaten in the company's interest, and at its expense.

I have a large and reasonably quiet office, and a private secretary who works for me alone, instead of part share in an overworked, underpaid, though invariably good-tempered and efficient, medical secretary.

I had expected to find the efficiency of commerce a change from the National Health Service's maladministration, but in this context my old and new jobs are strictly comparable. I really believe that in business there is more of penny-wisdom and pound (or thousand-pound)-foolishness, than in the N.H.S. itself.

There remains only one thing to add—the work is extremely interesting, perhaps even useful, and has rather less routine in it than any other job I have done.

Incidentally, in spite of all this plushiness, we are still served, at four in the afternoon and eleven in the morning, with the same terrible tea and appalling coffee.

* * *

She was a farmer's wife from the Fens, accustomed to good food and good living, and very free to express her thanks in the medium she knew best. Fortunately when she developed secondaries from breast cancer they responded to hormone therapy. Stilbœstrol did the trick and the years seemed to roll away as she lost her pain and regained her vitality. Being a mere male I naturally took the deluge of eggs which she presented to me as a tribute to the profession. Perhaps I should have known better.

The sad day came when stilbœstrol lost its magic. In despair I turned to testosterone. The pain went but so did the harvest of eggs. I found that Sister was getting them.

Letters to the Editor

CASUALTIES AND CASUALS

SIR,—The work underlying Dr. Fry's article of Jan. 16 prompts me to express warm approval. As chairman of a committee planning a new teaching hospital I have noticed more than once the different interpretations which various members of my committee place upon the word " casualty ". Some come to their first consideration of the planning of a hospital casualty department with memories of casualty-clearing stations, casualty lists, and the like. In fact they conform with Dr. Fry's observation that the word " casualty " implies " an accident or a serious or fatal event ". In an attempt to clarify this semantic confusion I have described a hospital casualty department as an " accident and emergency department ". An intractable epistaxis occurring when the family doctor is on his round and unavailable, an attack of renal colic when at work, a foreign body lodged in a small child's nose or ear, or a generalised convulsion in a child *is* an emergency from the patient's or parent's point of view, and no reclassification by doctors or administrators will prevent such cases presenting themselves with a sense of urgency at the hospital. The fact that their National Health Service family doctor might, if available, in many instances be able to deal with the situation does not detract from that sense of urgency. In any discussion of this subject agreement on this point is fundamental. If we are not to receive them in casualty in future what are we to do?

One alternative, as Dr. Fry seems to suggest in his discussion, is that some sort of selection of cases should be enforced. But by whom? Not by the porter on the door; surely only by the casualty officer; and that is what is happening now.

The issue is perhaps only confused when Dr. Fry writes " agreement has not yet been reached on the part that the casualty department should play ", and three lines (and one sentence) later " In my own series only 60% of cases were ' casualty ' problems . . ." Does he mean that only 60% were cases of " accident or a serious or fatal event ", or does he mean that only 60% were found, after careful examination by the casualty officer, to fit in to his present idea of what a casualty department should cater for? And anyway why " *only* 60% "? The figure is an index of the patients' diagnostic ability of their own urgent troubles and seems to me to be pretty good. I wish I could believe I could be 60% right in such circumstances.

From the medico-administrative or planning aspect of the casualty department of the future, three factors seem to be important but may be difficult to assess:

First, whether in any given neighbourhood the total number and rough distribution among diagnoses, ages, and sexes is likely to alter significantly. Dr. Fry's record of nearly double the number of new patients in 1958 as compared with 1946 is of interest here.

Secondly, whether the trend of any such change warrants a change in the selection of the persons (the consultants) in ultimate charge of casualty departments. For instance, would an orthopædic surgeon be peculiarly appropriate to deal with Dr. Fry's series of 2935 new patients in which 272 (9%) were fractures. The remainder (91%), we should notice, included sepsis, poisonings, various medical problems, soft-tissue trauma, burns, psychiatric problems, &c.

Third, whether we can anticipate any change in the pattern of general practice (group practice, health centres) which will cater for the 30% of cases immediately discharged and the 11% referred to their general practitioner.

I think that we need not agree with Dr. Fry that " the present-day casualty department has no specific function ". The patients who, as taxpayers, own it and pay for it evidently think it has. If we disagree with them and agree with Dr. Fry that the department is misused or abused it is up to us to suggest a remedy. Dr. Fry is probably wise to exclude such suggestions from his article.

In analysing the " referment " of these cases Dr. Fry raised another cogent point. Should a casualty department confine itself to first-aid and sorting? There are figures showing the distribution of the arrival of casualties over the 24 hours and from a study of these we have concluded that if the personnel is to be sufficient to cope really promptly and effectively with the " peaks " of accidents and " genuine " emergencies, there will be many idle hands in the department if no appointments for 2nd and 3rd attendances are given in the casualty department; if, in other words, referral is 100%.

It would seem sensible to re-define our casualty departments as " accident, emergency, and dressing-stations " and plan along these lines.

We should all feel indebted to Dr. Fry for his meticulous record-keeping and for his realistic appreciation of the difficulties and responsibilities of those in charge of a hospital's casualty department. His excellent paper will provide a basis for intelligent planning, and perhaps a challenge to revise the accepted ideas, if such there be, on junior and consultant staffing of casualty departments.

London, W.1. A. DOYNE BELL.

TREATMENT OF ADVANCED CARCINOMA OF THE BREAST BY OOPHORECTOMY AND PREDNISONE

SIR,—The paper by Dr. Brinkley and Dr. Pillers (Jan. 16) encourages us to place on record our experience with a similar regime at this hospital. Our series was started in June, 1956, and totals 46 cases. To date we have withheld publication in view of the small number of patients involved, the difficulty in assessing results, and the relatively short follow-up (three years and seven months).

We have found the age, menopausal status, and tumour-cell type to be of no help in predicting the outcome in any given case. An attempt to assess the degree of possible adrenal suppression has been made in all cases by serial estimations of urinary ketosteroid and œstrogen excretion levels. This has been a laborious procedure. So far as we can judge the fall in these levels bears no relation to the clinical results; that is to say, in some cases on whom a satisfactory remission has been obtained the levels of both remained within low normal limits.

The presence or absence of metastases in the ovaries also bears no relation to the outcome of the case. It has seemed to us desirable in selecting cases for oophorectomy to extend the upper age limit certainly to 65 years, and possibly later in a few others.

We have found it easier in most cases to demonstrate arrest of progress of metastases rather than objective evidence of regression. In a few patients large ulcerative lesions of the chest wall have completely healed and in others bony consolidation of deposits and regression of pulmonary lesions has definitely occurred. Symptomatic relief has, however, been common.

In this series we have not noticed any increased tendency to the formation of ascites, pleural effusion, or œdema of the arm as might have been expected with steroid therapy; rather in fact some patients who had required frequent chest aspirations of large pleural effusions for their comfort have ceased to require this procedure completely.

There are some disadvantages to this therapeutic programme. In the series there was one case of sudden death from massive hæmorrhage from an acute peptic ulcer and in one case not included in the series death occurred following perforation of a peptic ulcer. We have endeavoured to exclude patients with past histories of peptic ulceration or accepted them for treatment only after barium-meal examination. In all cases it has been our practice to prescribe routine alkali therapy with the prednisone. We have also excluded patients with active or only recently quiescent tuberculous lesions. It must be recognised that patients with associated diabetes mellitus present considerable therapeutic problems as a result of steroid therapy.

It is necessary to warn practitioners against the dangers of sudden withdrawal of the prednisone in patients who may develop an emergency condition.

In our 46 cases, 25 are now dead, 10 surviving less than six months; 8 obtained arrest of their disease for periods in excess of twelve months, 4 for two years and 2 for two-and-a-half years. It might be noted here that in 4 patients coming to necropsy when particular attention was paid to the adrenal glands, although there appeared to have been some reduction in their overall mass, no histological change had occurred.

Among the survivors still under treatment, 1 patient is alive and well after three years and seven months (she had a large fungating local recurrence in the chest wall, complicated by severe secondary hæmorrhages from the surface of the ulcer, which failed to respond to any other form of treatment). 1 patient is alive and well after three years, 1 at two-and-a-half years and 5 after twelve months. 6 patients have survived more than six months.

We feel that one must assess benefit not only by length of survival but also by the quality of the life lived by the patients in the interval before death. Even in some of our disappointing cases there is no doubt in our minds that distressing symptoms have been considerably ameliorated.

We feel that this regime is a valuable approach to the problem of the patient with widespread metastatic breast cancer when the only alternatives are adrenalectomy, hypophysectomy, or pituitary destruction. These are big undertakings, to the patient and surgeon alike; for on the one hand they are not without hazard and on the other, improvement cannot be promised with certainty in any given case.

It may suffice to say that since the evolution of this line of therapy bilateral adrenalectomy or hypophysectomy has been a very infrequent procedure at this hospital.

We are grateful to Dr. Cameron, of our biochemistry department, for his help with the endocrine estimations.

St. George's Hospital, London, S.W.1. ARNOLD ELEY
VICTOR RIDDELL.

A CENTRAL LABORATORY FOR OCCASIONAL INVESTIGATIONS

SIR,—I support Dr. Hughes-Davis (Jan. 2) in his suggestion for reference laboratories for occasional investigations, requests being referred by a pathologist.

In addition I should welcome contact with a special laboratory under the control of the National Health Service where one could obtain an occasional check of any of the more unsatisfactory routine estimations—e.g., serum uric acid, diastase, high bilirubins. A specialist laboratory should attract the necessary calibre of trained biochemists if adequate finances were available.

We now regularly use the freeze-dried serum prepared by arrangement with the Association of Clinical Pathologists, &c.; but this only, at present, allows the extra check of seven of the more simple estimations.

Fletcher Laboratory, Royal West Sussex Hospital, Chichester, Sussex. PHYLLIS DAGNALL.

INDUCTION OF ANÆSTHESIA IN YOUNG CHILDREN

SIR,—Dr. Hodges' thoughtful article (Jan. 9) is of interest to all who have the handling of children at heart. The difficulty in all this work is to devise an absolute standard of behaviour pattern. Doughty [1] first drew attention to this need, and he has done much work since. Using a similar classification to his I did a controlled series of 100 cases, comparing premedication with atropine only, with a methylpentynol/hyoscine mixture given by mouth. A summary of my results was:

Reaction	Premedication: Atropine only	Premedication: Methylpentynol/hyoscine
Smiled	5	12
Impassive	18	26
Winced	16	2
Cried	11	10
Total	50	50

All cases were induced with intravenous thiopentone.

I still feel that we should help the "self-controlled but guarded" cases of Dr. Hodges, provided this can be done with safety, and for this purpose I still find the methylpentynol/hyoscine mixture valuable.

Recent correspondence in the *Medical Journal of Australia* [2–5] again raised the matter of the incidence of vomiting during induction after premedication with methylpentynol in the form of 'Oblivon' elixir.

Rendell,[6] in the first article on the clinical use of methylpentynol, did state "in about a tenth of the cases induction . . . was delayed by vomiting". It is unfortunate that this statement has been copied many times, including in the new textbook on anæsthetics by Wylie and Churchill-Davidson, because on closer reference to Rendell's article it is stated that "though normally premedication was given 1 hour before operation, half to 2 hours or more proved satisfactory".

In my original article,[7] in which I quote from over 500 cases, I stated that ". . . no difficulty from vomiting on induction has been observed. I think the difference in my series is due to the fact that the methylpentynol had been given at least 1 hour before induction".

I. R. McDonald stated [3] that he passed a Ryle's tube on 4 successive cases premedicated with this drug and that the minimum volume aspirated was 8 oz. (230 ml.).

This obviously needed verification. During routine tonsil lists I therefore passed a small plastic œsophageal tube under direct vision after the patient had been induced and was on the table with the Boyle-Davis gag in position. The presence of the tube in the stomach was confirmed by auscultation over the epigastrium. The following were my results:

Age (yr.)	Premedication: Elixir oblivon (drachms)	Premedication: Hyoscine (gr.)	Time given	Time of aspiration	Volume
10	4	1/100	8·45	10·15	1 ml.
3	2	1/150	8·45	10·15	nil.
7	3	1/100	8·45	10·45	nil.
7	3	1/100	9·0	11·10	nil.
6	3	1/100	9·15	11·30	nil.
12	4	1/100	8·30	10·0	10 ml.
6	3	1/150	8·45	10·15	nil.
5	2	1/150	9·0	10·40	1 ml.

In no case was the stomach aspirated less than $1^1/_2$ hours after the premedication: this I am sure is the secret of success with this method. The hyoscine is dissolved in the methylpentynol so that no preoperative injection of atropine is necessary. I still find this a very safe and satisfactory premedication for children.

Worthing. F. R. GUSTERSON.

SIR,—Dr. Hodges' article prompts a few reflections from me. As an early worker on the effects of hospital on young children I noted that "the operation for the removal of tonsils seems to be very traumatic, out of all proportion to its severity".[1] It was therefore very reassuring to note how, with modern methods, the trauma of the anæsthesia and the surgery could be reduced to a minimum.

I was the more interested however in Dr. Hodges' other finding—namely, that "factors other than anæsthesia may be more often responsible for psychic trauma", and he specifically mentions homesickness. This would correspond to the psychiatrists' "emotional insecurity" (or overdependence) a feeling which, as explained in my monograph, is the key to the whole problem of hospitalisation. One does not so much ask for special methods in hospital; I take it for granted that every effort is made to minimise the unpleasantness of the procedures there. But one must always be prepared to find a few children for whom *the hospitalisation itself* is the distressing experience. These are the potential cases of neurosis and may need added or special attention. The majority of children, with normal sympathetic handling, "digest" and overcome the experience: not so these few who fail on account of some inner problem making them the more vulnerable.

Leeds. H. EDELSTON.

CONTROL OF ANTICOAGULANT THERAPY

SIR,—Dr. Matthews and Dr. Walker (Dec. 26), referring to the one-stage prothrombin-time, state: "It is familiar to clinical pathologists and hospital doctors in general who, despite its theoretical and practical shortcomings, have confidence in the method and find it tolerably safe." Such a statement impugns not merely the reliability of the original test but also that of other procedures, especially the thromboplastin generation test, since the last step in the latter method is essentially a one-stage prothrombin-time.

What are the theoretical shortcomings?

The one most commonly cited is that a prolonged prothrombin-time is generally not due to a decrease of prothrombin. When the test was developed, such factors as thromboplastin and prothrombin were recognised primarily as activities, and it was found by both the one- and two-stage methods that the level of prothrombin in the blood markedly dropped in vitamin-K deficiency and after the administration of dicoumarin. With the observation [2] that the delayed prothrombin-time of stored oxalated human plasma could be completely corrected by the addition of fresh plasma depleted of prothrombin by adsorption with $Al(OH)_3$ or plasma from an animal given dicoumarin, it became evident that the test was also sensitive to a new clotting factor hitherto unrecognised. It is now established that the test is not only sensitive to this factor (labile or V) but also to stable factor (VII) and to the less well-defined Stuart-Prower factor. By adding to the patient's plasma a minute amount of labile factor in the form of deprothrombinised rabbit plasma, the prolonged prothrombin-time in congenital labile-factor deficiency is corrected to the normal of 12 seconds. Likewise, the prothrombin-time is corrected to 12 seconds by the addition of normal aged serum in stable and in Stuart-Prower deficiency.

Only in true hypoprothrombinæmia is there no correction effected by either adsorbed rabbit plasma or aged serum. Thus, by simple modifications of the one-stage method, it can be made specific for any of the known factors in the prothrombin complex. What is called a shortcoming is actually a pillar of strength. The newly alleged shortcoming—namely, that it is not sensitive to the contact factor—would, no doubt, be serious if we had glass-lined blood-vessels.

Interestingly, Matthew and Walker found a good correlation between the thrombotest and the Quick test while the "correla-

1. *Brit. J. Anæsth.* 1957, **29**, 407.
2. McDonald, I. H. *Med. J. Aust.* 1959, ii, 417.
3. McDonald, I. R. *ibid.* p. 541.
4. McDonald, I. H. *ibid.* p. 740.
5. Gusterson, F. R. *ibid.* p. 829.
6. Rendell, C. M. *Brit. med. J.* 1954, ii, 1397.
7. Gusterson, F. R. *Lancet*, 1955, i, 940.

1. Edelston, H. Separation Anxiety in Young Children. Genetic Psychology Monographs, 1942.
2. Quick, A. J. *Amer. J. Physiol.* 1943, **140**, 212.

tion between thrombotest and the P & P test was not quite so good". Yet, only a relatively short time ago, the latter test was introduced as a much superior test to the basic one-stage method. The logic of how all this is likely to "confirm it (thrombotest) as the best laboratory procedure for the control of anticoagulation therapy" is somewhat elusive.

Department of Biochemistry,
Marquette University School of Medicine,
Milwaukee, Wisconsin. ARMAND J. QUICK.

CHROMOSOME STUDIES IN LEUKÆMIA

SIR,—The calculations for 8 cases of chronic leukæmia (3 myeloid and 3 lymphatic) referred to in our letter of Jan. 16 are shown in the accompanying table.

DISTRIBUTION OF CHROMOSOMES COUNTS IN CHRONIC LEUKÆMIA

	Patient	<44	44	45	46	47	48	>48	Totals
Chronic myeloid leukæmia	H51	0	1	6	36	2	2	0	47
	H61	0	1	0	22	0	1	0	24
	H73	0	2	4	16	0	0	0	22
	H229	0	3	0	15	0	0	0	18
	H237	1	2	3	26	0	0	0	32
	Total	1	9	13	115	2	3	0	143
Chronic lymphatic leukæmia	H82	2	0	0	19	0	0	0	21
	H238	0	0	4	27	1	0	0	32
	H250	2	1	1	16	1	0	0	21
	Total	4	1	5	62	2	0	0	74

		Modal	Non-modal	χ^2	P (n = 1)
C.M.L.	Expected	121·6	21·4	2·40	>0·1
	Observed	115	28		
C.L.L.	Expected	62·9	11·1	0·09	>0·7
	Observed	62	12		

Medical Research Council Group for Research on the General Effects of Radiation,
Western General Hospital,
Edinburgh.

A. G. BAIKIE
W. M. COURT BROWN
PATRICIA A. JACOBS.

NATURAL HISTORY OF CAVERNOUS HÆMANGIOMATA

SIR,—We are discussing a very little understood condition, which in some ways might be classed with congenital deformities, and in others with new growths. May I suggest a name for it which I have used for many years—"the spreading angioma of infancy"? Nævus is a meaningless term, including stains and moles; "strawberry" as an adjective applies only to minor degrees; and there is nothing in them resembling caverns. But they do belong to the vast and varied group of angiomata, they do grow, and this growth does occur in infancy.

I wrote about one stage in the natural history of one type of these angiomata, the small but growing spot on the face which appears at or soon after birth. They are often described by the mothers, who alone at this stage worry about them, as having started like a gnat-bite or a little scratch. They are seen by general practitioners, doctors in clinics, pædiatricians, and obstetricians; but I have never known them at this stage to be referred to dermatologists or plastic surgeons. This correspondence has made it clear what would happen if they were. What they are apt to grow into is shown by the accompanying photographs, and the question I raised was whether this horrible development could be stopped.

It must be clearly understood that it is not treatment at the stage illustrated which I am discussing, but treatment to avoid its occurrence.

On the comparatively rare occasions on which I find these growing red spots I have been treating them by subcutaneous injections of saturated salt (sodium chloride) solution, which is non-toxic but extremely caustic; if injected into the skin it will cause a slough. I get the impression that the violent cellular reaction produced in the deep tissues by this will begin the process of regression; at any rate none treated in this way has run wild as they so often do if left alone. Supposing one were to get a hundred of these "surgical emergencies"—the growing red spots on the face—treat them with these injections, and find that there were no disfigurements of the kind shown, one would have some interesting though inconclusive information. It would be inconclusive because it would be impossible to prove what would have happened had nothing been done; but then so much medical information is of this type.

I have also been pleased with the results of injecting comparatively large quantities, up to 5 ml., into that type of angioma which closely mimics a rapidly growing sarcoma of the face; a deep elastic swelling with a faint blue tinge, under skin which at first is intact. This type again is not referred to dermatologists or plastic surgeons; it sets difficult problems of diagnosis and treatment to the general surgeon.

As to other methods of treatment, I dislike X rays, though they are undoubtedly effective during the period of rapid growth. Carbon-dioxide snow is obviously completely futile on any but the very superficial types which are best left alone. A primary excision is often the best as well as the most obvious treatment; it saves the mother years of embarrassment, and in

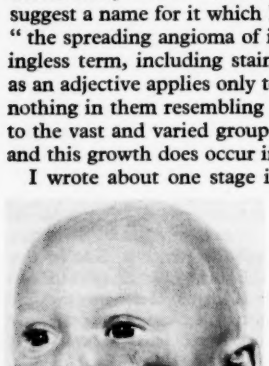


Fig. 1

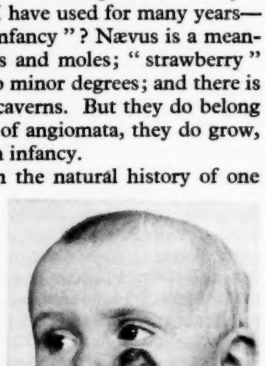


Fig. 2

Fig. 1—Angioma at stage of full growth, and beginning regression. Started as small spot, will end as mass of redundant fibrous tissue.

Fig. 3—Similar case to figs. 1 and 2, showing a more advanced stage of regression, with a baggy scar of the cheek.

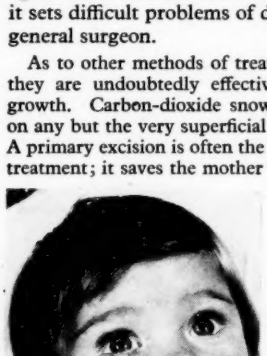


Fig. 3

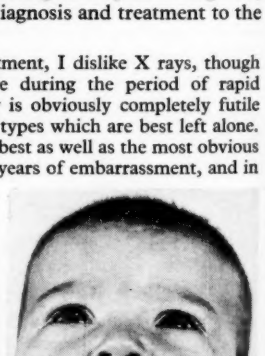


Fig. 4

Fig. 2—Similar case to fig. 1.

Fig. 4—An angioma at the stage of rapid growth, showing many points at the "gnat-bite" stage. It is obvious that bad scarring will result, and excision of the redundant tissues of the lip be necessary.

any case often has to be done on the sagging mass of fibrous tissue left when regression is complete.

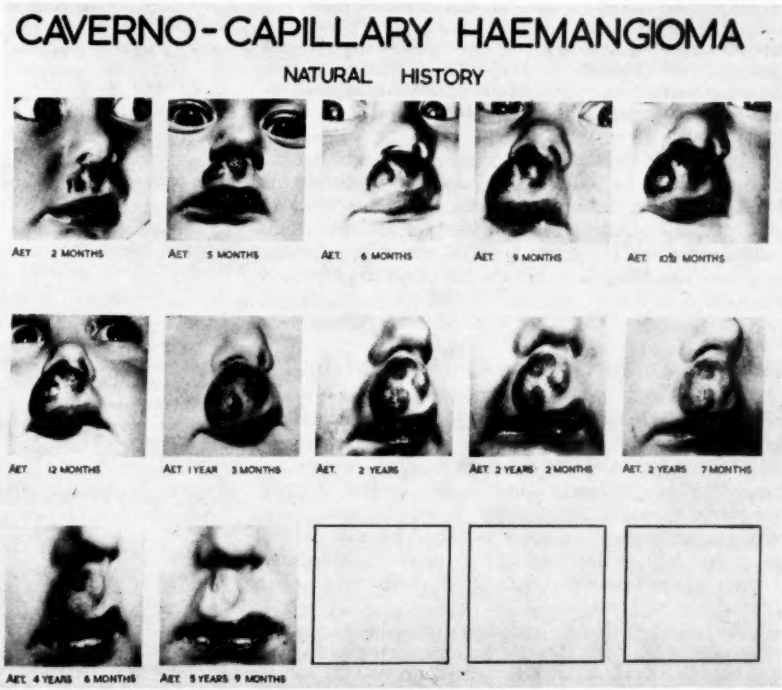
The substances used for sclerosing veins are unsuitable, being too toxic in the tissues. The diathermy needle, insulated except for its point, is useful, but I have been afraid of injuring a nerve with it.

But I realise that a concerted investigation of the kind I have suggested is impossible in the present fragmented state of my profession.

London, W.1. DENIS BROWNE.

SIR,—I have been very interested in the extensive correspondence on this subject, which was also debated at some length at a meeting of the Dermatological Section of the Royal Society of Medicine held at The London Hospital on June 18, 1959.

My experiences conform closely to those of Dr. Simpson (Dec. 12) and I also follow Mr. Murley's plan (Jan. 9) of showing photographs to the parents.



Some of your readers may be interested to see a series I collected in the past six years—not yet complete but very valuable for indicating to an anxious mother that Nature is on the side of recovery. The large hæmangioma has disappeared at 5 years 9 months, leaving a residual soft fleshy excess of tissue which it is anticipated will disappear within the next few years. The three blank spaces are for later photographs.

Acknowledgment is due to the photographic department of The London Hospital.

London, W.1. BRIAN RUSSELL.

SIR,—In view of Dr. Simpson's series and other meticulously followed-up and carefully analysed series illustrating the natural history of cavernous hæmangiomata, it astonishes me to find that anyone can strongly disagree, as Dr. Millington (Jan. 16) does, with these findings, which have been amply confirmed by the vast majority of dermatologists and plastic surgeons, when his sole criterion of satisfaction regarding his series of 1000 irradiated children is that "in a confined community such as this one would expect to be made aware of any untoward sequelæ of treatment".

Quite apart from unhappy sequelæ of irradiation, which Mr. McLaughlin (Jan. 16) so rightly deplores, Dr. Millington's statement about "doubtful hopes of natural resolution" is in no way supported by the facts.

Princess Margaret Hospital, Swindon. K. D. CROW.

SIR,—Dr. Simpson's article on strawberry nævi and the subsequent correspondence have interested me greatly. I have studied 152 consecutive children with 191 strawberry nævi, first seen between 1950 and 1953. Particular care was taken to make the follow-up as complete as possible, and the 9 children who were untraced are all known to have moved away from the district. It is unlikely that they would have done this simply to seek surgical aid. The results, which are being prepared for publication, are in complete agreement with Dr. Simpson's and lend strong support to the view that conservative treatment is the best policy.

Gloucestershire Royal Hospital, Gloucester. R. E. BOWERS.

HYDROFLUMETHIAZIDE

SIR,—With great interest I read the article[1] by Dr. Edmonds and Professor Wilson. A brief remark on p. 308 deserves attention because it may contribute to removing the confusion which seems to prevail regarding the conception of the kaliuretic effect of the various derivatives of chlorothiazide and its theoretical background. It reads: "Hydroflumethiazide also possesses the sulphonamide group, and probably its lack of effect on bicarbonate excretion results from the much smaller quantity used."

Hydroflumethiazide and hydrochlorothiazide have a chloruretic effect which is about 15 times greater than that of chlorothiazide; as a consequence when using them the quantity of sulphonamide supplied is about 15 times smaller than when using chlorothiazide, to obtain a certain chloruretic effect. Consequently the excretion of bicarbonate and therefore the kaliuresis are smaller. However, it is doubtful whether these differences in "the primary kaliuretic effect" are of any therapeutic importance. Experience shows that a potassium supplement is often necessary in prolonged treatment with all existing preparations of this group of diuretics, and it is very probable that the potassium loss is more closely connected with their chloruretic effect, as is the natriuresis; whereas the kaliuresis which is connected with the inhibitory effect on carbonic anhydrase is relatively small in comparison (although it is of course the smaller the less sulphonamide they contain in proportion to their chloruretic effect).

Of far greater therapeutic importance is undoubtedly "the secondary kaliuresis", which in certain patients may arise after

1. *Lancet*, 1959, ii, 303.

administration of all potent diuretics with natriuretic effect, and which is a consequence of the increased secretion of aldosterone initiated by the organism as a " defence " against the increased natriuresis (as well as against too rigorous restrictions of salt in the diet). Recognition of this condition, and its treatment, are only in the embryo stage, but the introduction of spirolactone opens a wide field.

A great deal of unnecessary discussion as to whether one diuretic should be preferred to another, especially with reference to the kaliuretic effect, might, however, be avoided if we (1) keep this quantitative situation of the sulphonamide group in mind, and (2) in each individual case try to establish whether the kaliuresis is primary or secondary.

Hillerød, Denmark. TORBEN ANDERSEN.

FRUCTOSE TREATMENT OF PHENYLKETONURIA

SIR,—Some of our patients suffering from phenylketonuric oligophrenia have not been able to keep to their low-phenylalanine diets for various reasons. Geisler and Ströder [1] reported that they were able to increase the phenylalanine tolerance and decrease the phenylketonuria of such patients by giving fructose intravenously or orally. In order to see if fructose feeding (6 g. per kg.) would help our patients we tested two known phenylketonurics who have been receiving a normal diet at home.

CASE 1.—A boy (H.S.C. 208562) aged 8 years was first seen at the age of $2^1/_2$ years suffering from frequent fits, deafness, and mental backwardness. His general I.Q. was 20 and his plasma contained 30 mg. per 100 ml. phenylalanine and his urine contained phenylpyruvic acid. Although treatment with a low-phenylalanine diet was started and his general I.Q. rose to 30, he failed to keep to the diet and has received a normal diet for the past four years (general I.Q. now 13).

CASE 2.—A girl (H.S.C. 265841) aged 5 years was first seen at the age of 2 years because of frequent fits and mental retardation. Her general I.Q. was 20, plasma-phenylalanine 30 mg. per 100 ml., and her urine contained phenylpyruvic acid. After eighteen months' treatment with a low-phenylalanine diet the general I.Q. rose to 30 and then remained stationary when the diet was not being adhered to. For the past eight months a normal diet has been taken and the general I.Q. has fallen to 20 again.

Each patient was fed on (1) a normal diet, (2) the same normal diet except that fructose 6 g. per kg. daily was substituted for all the sucrose or glucose normally taken, and (3) a normal diet again. The fructose supplied all the sugar that was needed in the diet. Plasma levels of phenylalanine were estimated by the comparison of paper chromatograms of known standards and desalted plasma. Urine phenylpyruvic-acid levels were estimated by the method of The, Fleury, and Vink.[2] The results are shown in the accompanying table.

Bearing in mind the fluctuations in daily urine phenylpyruvic-acid excretion, it is seen that fructose feeding was not associated with any marked changes. Plasma-phenylalanine levels also were not affected favourably. Close observation in the ward showed that no changes in behaviour in either patient were associated with fructose feeding (Mr. Stephen Coates).

Fructose feeding does not appear to have been of use in the treatment of these two patients suffering from phenylpyruvic oligophrenia.

We should like to thank Mrs. M. B. Hummerston, of the dietetic department, Sister E. M. Baldwin, of the metabolic ward, and Mr. Stephen Coates, senior clinical psychologist, for their invaluable help in this investigation.

Institute of Child Health and The Hospital for Sick Children, London, W.C.1. A. A. MONCRIEFF R. H. WILKINSON.

1. Geisler, Von E., Ströder, J. *Ann. pædiat.* 1958, **191**, 147.

EFFECT OF FRUCTOSE DIET ON PLASMA-PHENYLALANINE AND URINE PHENYLPYRUVIC-ACID LEVELS

Case	Diet	Plasma-phenylalanine (mg. per 100 ml.)	Urine phenylpyruvic acid
1	Normal diet for the past 4 years, tested for 4 days	30	100–400 mg. per 100 ml.
	Fructose substitution (120 g. per day) for 14 days	30	100–400 mg. per 100 ml.
2	Normal diet for past 8 months, tested for 4 days	30	70–200 mg. per 24 hr.
	Fructose substitution (120 g. per day) for 8 days	50	50–220 mg. per 24 hr.
	Normal diet for 21 days	—	50–500 mg. per 24 hr.
	Fructose diet for 19 days	First day 50	Ferric-chloride test *strongly positive* daily
		Last day 50	

REMOVING A SAFETY-PIN FROM THE BRONCHIAL TREE

SIR,—Would I be wrong in suggesting that Chevalier Jackson demonstrated Mr. Donald Barlow's device (Jan. 23) for removing an open safety-pin from the bronchial tree some 30 years ago?

The story was told in America that when Chevalier Jackson was tossing open safety-pins into an anæsthetised dog's trachea, a mild little man at the back of the room asked if he could have a go. He mastered the technique, caught the night train, and removed the open safety-pin from the trachea of his infant patient.

London, W.1. W. HARGRAVE-WILSON.

KEROSENE (PARAFFIN) POISONING

SIR,—Ingestion of kerosene (paraffin oil) is a common cause of accidental poisoning, particularly in children. Recent animal studies by the Medical Research Division of Esso Research and Engineering Company, Linden, New Jersey,[3] have shown that kerosene poisoning is principally due to aspiration of the material into the lungs, where the kerosene produces a chemical pneumonitis. The volume of kerosene required to produce a pneumonitis is very low: thus, kerosene by aspiration into the lungs is highly dangerous. By contrast, large amounts of kerosene can be ingested without pulmonary injury or ill effect.

The accompanying table shows the oral toxicity of common liquid chemicals.

ORAL TOXICITY OF COMMON LIQUID CHEMICALS

Chemical	L.D.$_{50}$ (mg. per kg.)	Toxicity class
Acetic acid (rat)	3310	Slightly toxic
Lactic acid (rat)	3730	Slightly toxic
Isopropyl alcohol (rubbing alcohol) (rat)	5840	Practically non-toxic
Acetone (rat)	9750	Practically non-toxic
Ethyl alcohol (rat)	13,660	Practically non-toxic
Glycerine (rabbit)	27,000	Relatively harmless
Kerosene (rabbit)	28,350	Relatively harmless

If oral toxicity is low (high L.D.$_{50}$) the probability of systemic intoxication is low and removal of kerosene from the stomach is unnecessary.

Clinical kerosene poisoning is probably due to aspiration of a relatively small volume of kerosene during or shortly after swallowing rather than to blood-borne kerosene absorbed

2. The, T. P., Fleury, P., Vink, C. L. J. *Clin. chim. acta*, 1957, **2**, 424.
3. Gerarde, H. W. *Delaware St. med. J.* 1959, **31**, 276.

from the gastrointestinal tract. Since the oral toxicity of kerosene is low, the treatment should not include the induction of vomiting or other clinical procedures such as passage of a stomach tube for gastric lavage which may induce vomiting and thus aspiration. (The present teaching in the first-aid manuals of the various societies is "Make the casualty vomit. Give copious draughts of water.") Since anti-emetics are central-nervous-system depressants, they are contraindicated because sedation and stupor are frequently found in kerosene poisoning. Positive measures recommended are (1) oxygen if necessary; (2) antibiotics prophylactically, for the prevention of secondary bacterial pneumonia; (3) if the patient is conscious, ingestion of a vegetable oil or ice-cream to dilute the kerosene, diminish the rate of absorption into the blood, and soothe the inflamed mucous membranes of the gastrointestinal tract.

Esso Petroleum Co., London, S.W.1. ERNEST H. CAPEL, Chief Medical Officer.

Esso Petroleum Co. Fawley. A. WARD GARDNER, Senior Medical Officer.

THE PREP SCHOOL

SIR,—I was most interested to read the admirable review of the I.A.P.S. report *Foundations* in your issue of Jan. 2. In it you refer to the difficulty of finding suitable masters, and I thought you might be interested to know the steps that our Association takes to train those who teach in its schools.

A joint committee of I.A.P.S. and the Oxford Institute of Education runs an eighteen-month training course on a correspondence basis with four short residential periods. This is for young men and women who have recently taken up teaching. In 1958 and in 1959 we put on a week's residential course at Oxford for men leaving the Services and intending to teach in our schools. These courses had the approval of the Resettlement Board and were so successful that we hope to run another this year.

Residential refresher courses are held for a week every April in Oxford for headmasters and their staffs, to ensure that the latest developments and methods in education are brought to their notice.

Swanbourne House School, Swanbourne, near Bletchley, Bucks. H. A. C. EVANS, Chairman, Incorporated Association of Preparatory Schools.

LEISHMANIASIS ACQUIRED BY CONTAGION

SIR,—Professor Symmers is to be congratulated on his paper of Jan. 16 which has made history, and is moreover most intriguingly and fascinatingly written. It certainly gives rise to new appraisals and causes students of this subject most furiously to think.

The outstanding facts are that it is possible for a man suffering from *Leishmania donovani* infection to pass it on by sexual intercourse to his wife, thus producing a local lesion in the vagina, to all extent and purposes resembling an oriental sore (attributable to *Leishmania tropica*). At first sight this course of events suggests that current beliefs need revising. However, there may well be another explanation in the true ætiology in the analogy of Kenya kala-azar, where cultures of *L. donovani* isolated from the gerbille, *Tatera vicina*, in the leptomonas stage, when inoculated subcutaneously into volunteers, gave rise to a local lesion, known as a leishmanioma.[1] This is probably analogous to the primary lesion of epidemic kala-azar and which was first described by Clinton Manson-Bahr [2] in North Kenya. It is from this leishmanioma on the tibiæ that the organisms spread throughout the body to subsequently produce the classical picture of visceral leishmaniasis (or kala-azar).

But more disturbing than this, from the viewpoint of the student of tropical medicine, is the recital of what may be called "a tragedy of errors". It is a sad commentary on the efficacy of the ancillary services of present-day medicine. From the viewpoint of the consultant in tropical diseases I would venture to suggest that these avoidable mistakes arise primarily from the neglect of the fundamental principles of clinical medicine—the taking of a case-history. How often one observes that the obvious diagnosis has been missed by neglect to do so; to find out, for instance, whether the patient has recently come from the tropics, subtropics, or other foci of endemic disease. It is perfectly correct to state that the incidence of tropical infections has been much reduced, but it does not mean that they have been entirely swept away.

London, W.1. PHILIP MANSON-BAHR.

PREVENTION AND TREATMENT OF BEDSORES BY SILICONE CREAM

SIR,—Much work has been done with silicone creams and emulsions in the prevention of bedsores. Controlled trials showed that emulsion or cream must contain 20% silicone to be effective.[1] Products with less than 20% silicone were ineffective, and additional silicone over 20% did not increase the efficiency of the cream or emulsion.

Silicone emulsions in the prevention and treatment of bedsores have now been used by the district nurses in Flintshire since 1954 with very good results. They have the following advantages: (*a*) they are more effective than soap, water and spirit; and (*b*) they show a considerable saving of nursing time in the treatment of pressure-points. Recently two new silicone preparations have been given a trial in this county and have proved more effective than plain silicone emulsion.

One cream (bedsore cream I) contained 20% silicone fluid MS200, 0·05% phenylmercuric dinaphthylmethane disulphonate ('Penotrane'), and 0·5% dienœstrol. The other (bedsore cream II) contained the same amounts of silicone and penotrane but omitted the dienœstrol. Both creams were of pH 4·2, approximating to that of normal skin.[2]

District nurses who had considerable experience of silicone emulsions tried each of these creams in a number of patients. The record cards kept by the nurses show that both creams were more effective than plain silicone emulsions in the prevention and treatment of bedsores. Ten patients were treated with cream II (penotrane/silicone cream) and eight with cream I. Cream I seems more effective but it is only fair to emphasise that the number of cases treated so far is small.

The advantages of the new cream can be summarised as follows:

(1) They produce more rapid healing of damaged skin over pressure-points than do plain silicone emulsions.
(2) They appear to be more effective in penetrating the skin, and more efficient in protecting the skin of incontinent patients.
(3) They are easy to apply and repeated applications do not tend to "cake" on the skin.

As many hospitals and local health authorities are now using silicone emulsions, these small trials with the new silicone creams might be of interest.

The two creams used in the trial were kindly supplied by Messrs. Ward, Blenkinsop, from whom the plain penotrane/silicone cream is now commercially available. The cream containing penotrane and dienœstrol is only available for clinical trials at present.

County Health Offices, Mold, Flintshire. G. W. ROBERTS.

1. Manson-Bahr, P. E. C. *Trans. Roy. Soc. trop. Med. & Hyg.* 1959, **53**, 123–126.
2. Manson-Bahr, P. E. C. *ibid.* 1956, **50**, 465–471.

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DENTAL CARIES

SIR,—I was very pleased to see in your leading article of Jan. 16 that the importance of Stack's protein is recognised, as well as its significance in relation to the observations that caries is primarily a deficiency disease. (The term "Stack's protein" is preferable to "soluble protein" as it is only soluble under pathological conditions.) Indeed, there is now sufficient evidence available for one to be still more precise about the mechanism of the carious process.

You state that "about equal quantities of each type of protein are present in the interprismatic spaces, and the soluble protein is assumed to be the first part of the tooth substance to disappear". It is not quite clear what is meant by "interprismatic spaces". The electron-microscope photograph (fig. 1) shows the distribution of the two proteins in dental enamel before calcification. The denser keratin is in the prism walls and Stack's protein in both prism core and interprismatic regions.[1] When calcification occurs, apatite crystallites are deposited in, and protected by, both proteins.[2] Professor Darling and his coworkers have shown that the first stage of the carious process is the degradation and/or solution of Stack's protein.[3 4] This presumably exposes its apatite crystallites to further attack, and fig. 2 shows the state of affairs in chalky enamel, which is the second stage of the carious process. Here the prism walls remain normal, but without Stack's protein the crystallites which had been protected by it have mostly gone.

It seems probable that the stability of the protein is determined at the time of its polymerisation,[5] and that vitamins or trace elements act as catalysts in the process. There is abundant evidence from all parts of the world to show that the incidence of caries is related to diet. Lady Mellanby [6] showed that vitamin D, which reduces the incidence of caries, affects the matrix, and the paper quoted on vitamin B_6 [7] shows that other vitamins have to be considered too. Clinically it is known that fluorine causes a very substantial decrease in caries incidence, and experimentally Darling and Brooks [8] have shown that fluorine also modifies matrix production. At present there is not sufficient evidence to show whether caries is primarily a vitamin deficiency, a fluorine deficiency, or a combination of the two; but there is nothing against the belief that fluorine is the more important.

1. Little, K. *J. R. micr. Soc.* 1959, **78**, 58.
2. Little, K. *J. dent. Res.* 1957, **36**, 815.
3. Darling, A. I. *Brit. dent. J.* 1958, **105**, 119.
4. Darling, A. I., Mortimer, K. V. *J. dent. Res.* 1959, **38**, 1226.
5. Little, K. Proceedings of 4th International Conference on Electron Microscopy, 1958.
6. Mellanby, M. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1934, no. 191.
7. Strean, L. P., et al. *N.Y. St. dent. J.* 1958, **24**, 133.
8. Darling, A. I., Brooks, A. W. *J. dent. Res.* 1959, **38**, 1226.

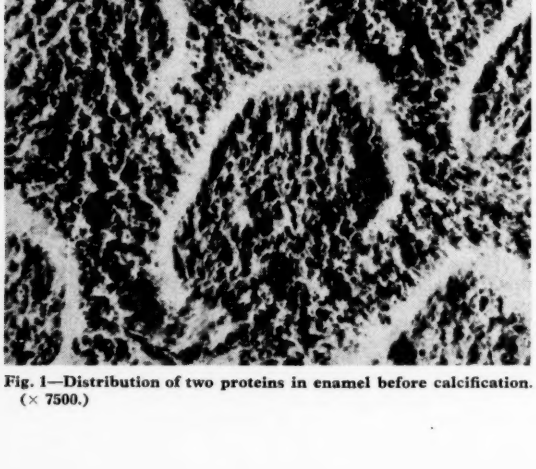

Fig. 1—Distribution of two proteins in enamel before calcification. (× 7500.)

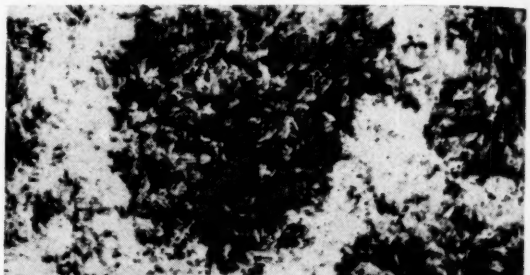

Fig. 2—Chalky enamel, the second stage of the carious process (white object on black background). (× 7500.)

The other main factor which is a practical consideration in the prevention of caries is the prevention of solvents from reaching the vulnerable protein. In perfectly formed teeth this is achieved by means of the surface zone. But it is of interest to remember that there are many instances of the surface zone being worn away in "uncivilised" communities without caries resulting. Acids and oxidising agents are undoubtedly partly responsible for caries; but when one examines critically the evidence for bacteria and refined sugar, traditionally regarded as causative factors, their claim seems to be curiously elusive. The bacteria appear in large numbers only after the carious process has been initiated. They are very probably more resistant to degradation than Stack's protein, so that it is worth considering whether components of toothpastes aimed at bacterial degradation are not even more likely to affect the Stack's protein, if this is exposed by abrasion or attrition.

Nuffield Orthopædic Centre,
Oxford. K. LITTLE.

TREATMENT OF CUSHING'S SYNDROME

SIR,—Dr. Montgomery and his associates [1] have commented on this very important problem by describing the occurrence of large pituitary tumours (one malignant) after adrenalectomy in 2 cases of their own and by collecting similar cases from the literature. They conclude that "... possibly in the future we shall have to consider hypophysectomy as an alternative to adrenalectomy more often than we do at present".

On the basis of 36 years' experience with the many aspects of Cushing's syndrome (my first case observed in 1923 was included by Cushing in his original description of the disease entity named after him [2]), I should like to offer yet another alternative—hands (that is, surgical hands) off the majority of patients who fall under this, of late, very loose heading. Of course I do not wish to imply that patients who are suspected of harbouring a carcinoma or even an adenoma of the adrenal cortex should be kept from surgery. I am referring to the vast majority of patients who have no evidence (e.g., in air-insufflation studies) of a gross adrenocortical lesion, unilateral or bilateral, or the full-blown clinical symptomatology, or at least gross hypertension which by itself may justify operation. In such patients the presenting symptom is commonly the characteristically distributed obesity with moon face and purple striæ associated with mild to moderate hypertension and/or diabetic tendencies (often very unstable) and with little or no abnormality of steroid excretion. In these formes frustes an attempt may in my opinion be made with a rigid dietary regi-

1. *Lancet*, 1959, ii, 707.
2. Cushing, H. *Bull. Johns Hopk. Hosp.* 1932, **50**, 137.

men, supported by appetite depressors and possibly by the judicious use of dehydration. As I have often emphasised,[3–7] very satisfactory results can thus be obtained, comparable to the remissions after surgery. Of course, relapses do occur, but so they do after surgery; moreover, this conservative therapy can be repeated at will, without fear of untoward side-reactions. If the patient fails to respond, an attempt may and indeed should be made with X-irradiation to the pituitary region before surgery is considered.

I agree that this treatment is neither infallible nor ideal. Nevertheless, I was led once more to stress the conservative method in the treatment of Cushing's syndrome after reading Dr. Montgomery's paper, which illustrates not only the well-known risks of adrenalectomy—namely the Scylla of adrenal insufficiency and the Charybdis of a recurrence—but adds to this list the possible development of pituitary tumours which may necessitate yet another and certainly not harmless operation.

Jerusalem. HERMANN ZONDEK.

ELECTRIC SHAVERS AND EYE AFFECTIONS

SIR,—It is now widely conceded that various inflammatory conditions of the eye, and in particular, the conjunctiva, may well be initiated by microscopic fragments of dandruff which lodge in the eye during combing or brushing of the hair. I would draw attention to another and more potentially dangerous source of similar irritation and/or self-infection—the electric shaver. At least one well-known manufacturer advises users to remove the shaving " head " after shaving and " blow across it " to remove the dust, which is composed, in persons with facial seborrhœa or abnormally dry skin, of powdered skin (or " scurf ") and very small fragments of hair.

Many persons almost certainly blow right *into* the shaving head in order to more effectually dislodge the dust, thereby driving some of the dust into eyes, nose, and mouth.

When the possible cumulative effect is considered (this is done at least 365 times a year!) the effect on the lungs might also be considered.

Cheltenham. R. ST. C. ISON.

OVERDOSAGE OF PHENELZINE SULPHATE

SIR,—The manufacturers of 'Nardil' (phenelzine sulphate) state that this recently introduced drug provides " safe and effective treatment for the outpatient management of milder depressive illnesses ". The following emergency seems worth reporting.

A married man, aged 32, was admitted to hospital on Nov. 28, 1959, after taking an overdose of 16 tablets (400 mg.) of phenelzine sulphate. The psychiatric history indicated that during the preceding 12 months he had been increasingly anxious over the payment of hire-purchase commitments. Early in October, 1959, he was angry and disappointed on receiving what he considered was insufficient payment for overtime work. He became more anxious, and finally depressed over arrears in his hire-purchase payments. He then had a hysterical fugue and wandered to a village some 20 miles away. On returning home he was subsequently referred to two psychiatric departments in the area but opted out of treatment at each establishment. On Nov. 25, 1959, he became severely depressed and was preoccupied with the idea that he had let his wife and child down badly. He was given a supply of phenelzine sulphate tablets by his general practitioner and on the night of Nov. 26 took 16 tablets at once. Almost immediately he became gay and elated (" I felt champion ") but after some hours became acutely anxious about the possible consequences of his act. His wife took him to hospital where his stomach was washed out. Following this procedure he slept deeply for 24 hours. By Nov. 30 he was reasonably well.

This case suggests that the outpatient use of thymoleptic drugs may in fact not be without danger. It also seems to confirm that phenelzine is indeed a thymoleptic.

It would be interesting to know whether any of your readers have encountered similar cases and what, in general, is the contemporary trend of opinion concerning the outpatient control of medication with thymoleptic drugs.

Department of Psychological Medicine, Eastern District Hospital, Glasgow. A. BALFOUR SCLARE J. M. ATKINSON.

ANTIBODIES AGAINST ADENOVIRUSES

SIR,—Data about the incidence and type distribution of adenoviruses in Hungary [1 2] are slight. A serological survey, using the methods of complement fixation (C.F.) [3] and virus neutralisation, was therefore made on various human sera.

As an antigen a mixture of the first 7 types of adenoviruses obtained in tissue cultures was used. Neutralisation tests were made in Detroit-6 cell cultures, using adenoviruses of types 1 to 7 separately. A total of 1174 human sera were examined by C.F. and 148 by neutralisation test. Results of C.F. are shown in table I. The groups of serum samples were as follows:

TABLE I—RESULTS OF C.F. REACTION

Group	No. of sera tested	% of C.F. positive	Average titre
1	85	41 (*48·2%*)	1:8·8
2	61	15 (*24·5%*)	1:11·6
3	163	24 (*14·7%*)	1:4·8
4	117	16 (*13·6%*)	1:10·7
5	632	268 (*42·4%*)	1:5·6
6	116	56 (*48·2%*)	1:7·3
Total	1174	420 (*35·7%*)	1:6·5

Group 1.—Sera of children, mostly under 5 years, convalescent after an attack of poliomyelitis.

Group 2.—Sera of persons of 10 to 20 years, in hospital with pulmonary tuberculosis.

Group 3.—Students of 18 to 20 years of age called for medical examination before admission to the University Medical School.

Group 4.—Random serum samples from apparently healthy persons over 20 years of age.

Group 5.—Sera from patients under medical cure with a diagnosis other than disease of the upper respiratory tract.

Group 6.—Patients with acute respiratory disease.

C.F. titre values varied between 1:4 and 1:64 for the different groups, and the maximum incidence was within the range 1:4 to 1:8. This observation agrees with the results of others.[4] The proportion of positive sera decreased remarkably in those over 40–50.

For neutralisation tests some of the sera with positive C.F. reactions were selected from all 6 groups. The highest incidence

TABLE II—DISTRIBUTION OF NEUTRALISING ANTIBODIES IN 148 SERA AGAINST TYPE 1 TO 7 ADENOVIRUSES

Antibody against	Sera containing antibody
Type 1	93 (*62·8%*)
Type 2	81 (*54·7%*)
Type 3	52 (*35·1%*)
Type 4	59 (*39·8%*)
Type 5	65 (*43·9%*)
Type 6	65 (*43·9%*)
Type 7	73 (*49·3%*)

3. Zondek, H., Leszynsky, H. E. *Brit. med. J.* 1956, i, 197.
4. Zondek, H., Leszynsky, H. E., Zondek, G. W. *Ann. Endocr., Paris.* 1957, **18**, 959.
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6. Zondek, H. Die Krankheiten der Endokrinen Druesen; p. 569. Basle, 1953.
7. Zondek, H. Le Malattie delle Ghiandole Endocrine; p. 743. Rome, 1957.

1. Nász, I., Tóth, M., Lengyel, A. *Acta microbiol. hung.* 1958, **5**, 267.
2. Béládi, I., Kahán, A. *Orv. Hétil.* 1958, **99**, 224–226.
3. Takátsy, G. *Acta microbiol. hung.* 1955, **3**, 191.
4. Zaimann, E., Balducci, D., Tyrrell, D. A. J. *Lancet*, 1955, ii, 595.

of neutralising antibodies was observed against types 1, 2, and 7 of adenoviruses, while those against types 3 and 4 were found only very seldom (table II). As to the simultaneous occurrence of different antibodies against the first 7 types of adenoviruses in the sera tested, the following figures were obtained:

Against 1 and 2 types 19·5% and 18·2% incidence of antibodies was observed respectively. Against 3 and 5 types 16% and 17% of sera contained simultaneous antibodies respectively. The simultaneous occurrence of antibodies against 6 types was 9% and against all 7 types tested 2·7%.

The proportion of positives was highest in the age-group 31–40. Thus persons in this group apparently had the highest simultaneous incidence of antibodies against the 7 different groups of adenoviruses tested.

A more detailed presentation of our results will be published elsewhere.

Institute for Microbiology, University Medical School, Budapest.

I. NÁSZ
M. TÓTH.

MATERIAL FOR CUBICLE CURTAINS AND WARD SCREENS

SIR,—The modern trend of thought for patients' privacy has focused attention on materials suitable for curtains and screens. Whilst bacteriological reasons would appear to condemn these as dangerous, it is clearly desirable for workers to endeavour to find a suitable material.

The following problems had to be faced in evaluating the claims of fabrics:

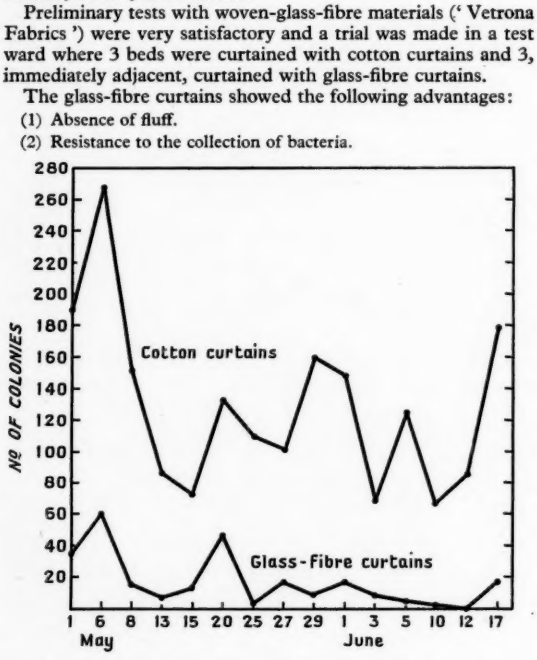
(1) Fluff: any material increasing the amount of fluff with its attendant carriage of bacteria is not acceptable.
(2) Resistance to the collection and release of bacteria in clouds when drawn or moved.
(3) Inflammability.
(4) Ease of hanging and washing.
(5) The electrostatic risk.
(6) Economy.

Plastic materials proved a problem from the electrostatic angle, and were difficult to change and clean. They became stained, brittle, and cracked.

Preliminary tests with woven-glass-fibre materials (' Vetrona Fabrics ') were very satisfactory and a trial was made in a test ward where 3 beds were curtained with cotton curtains and 3, immediately adjacent, curtained with glass-fibre curtains.

The glass-fibre curtains showed the following advantages:

(1) Absence of fluff.
(2) Resistance to the collection of bacteria.



Number of colonies from 3 cotton curtains and 3 glass-fibre curtains.

(3) Non-inflammable.
(4) Hung with nylon runners on a plastic rod, they were easily withdrawn and rinsed in ' Hytox ', 15 fl. oz. to a 15-gallon bath of water for 15 minutes, drained and rehung immediately.
(5) Non-electrostatic.
(6) Very economical, priced at approximately twice the cost of the usual cotton materials; only one set is required owing to saving in laundering; and resistance to wear appears much greater than with cotton.

Bacteriology

The accompanying figure shows the counts obtained in the test. As sweep plates were useless owing to the nature of the material, tests were made by making a hole in the bottom of an old petri-dish box. The agar plate was exposed in the inverted lid of the box, the curtain to be tested stretched over the lid, the box replaced into the inverted lid, thus stretching the material taut, a 5 g. weight dropped through the hole in the bottom, and 15 seconds allowed to elapse for bacteria to settle. After 48 hours' incubation all colonies were counted on the 3 plates taken from the 3 cubicles (i.e., 1 from each). These were taken between 10.30 and 11 A.M.

The upper line indicates readings from the 3 cotton curtains and the lower for the 3 glass-fibre curtains. On June 12 only 2 colonies were recovered from the 3 glass curtains after 6 weeks' use in an overcrowded gynæcological ward admitting many septic abortions. The curtains were not laundered, cleaned, or treated in any way during this test. Laundering of these curtains can clearly be left to intervals of several months if further trials confirm these results, and the saving of labour is therefore very great.

We are grateful to Messrs. Vetrona Fabrics Ltd., Sunnyside Mills, Bolton, Lancs, who made available to us the curtains for this experiment.

Department of Pathology, Little Bromwich General Hospital, Birmingham.

KEITH S. THOMPSON
MARY J. WEBB.

CHROMATOGRAPHIC ESTIMATION OF CORTICOSTEROIDS BY ^{14}C-LABELLED TETRASOLIUM SALT

SIR,—Often very small amounts of corticosteroids have to be determined in clinical and experimental work. The generally used reactions (tetrasolium-blue colour reaction and the " soda-fluorescens " procedure) are often unsatisfactory because of their low sensitivity (0·3–0·5 μg. per sq. cm.).

For the microdetermination of corticosteroids previously used methods were followed with isotope-labelled corticosteroids. In this way ^{14}C or ^{3}H corticosteroids could be measured by dilution or acetylation in the presence of acetic anhydride containing ^{14}C or ^{3}H. These methods raised technical difficulties, so we used ^{14}C-labelled tetrasolium salts (triphenyl-tetrasolium chloride and tetrasolium blue), which gave colour reactions with the corticosteroids. We then performed determinations with pure steroids. The tetrasolium-formazan produced could be separated easily from the superfluous tetrasolium chloride or tetrasolium blue on the basis of their dissolution relations (tetrasolium chloride and tetrasolium blue dissolve well in water, while the organic-soluble formazan does not).

For the detection a gas-flow GM-counter was used, by which we were able to measure 0·05 μg. of corticosteroid. According to our calculations, with a specific activity of 2 mC per g. and these detection techniques, the determination of about 0·01 μg. of corticosteroid is also possible. Our present work is designed to determine the corticosteroids in biological fluids.

Institute of Pathophysiology, University of Budapest.

PAUL WEISZ.

Central Research Institute for Chemistry of Hungarian Academy of Sciences, Budapest.

JOSEPH MÁRTON.

Institute for Organic Chemical Technology of Technical University, Budapest.

THOMAS GOSZTONYI.

RED-CELL DIAMETER IN INDONESIA

SIR,—Our investigations of red-cell diameter in our country show higher normal values of 7·39 μ (male: 7·38 μ, female: 7·40 μ).

The subjects for these measurements were 30 males and 10 females, all members of the staff of preclinical departments. They showed no signs of anæmia and hæmoglobin level, red-cell count, colour-index, packed-cell volume, and standard deviation were within normal limits.

The technique used was the microprojection method described by Price Jones, but a groundglass screen was used. With this modification, magnification of 5000 times is still clear enough to distinguish the erythrocyte's outlines sharply. 500 red cells were measured in each subject.

Although we obtained higher values for mean corpuscular volume (80·3–116·7 c.μ) which is not surprising, we also obtained lower values for mean corpuscular hæmoglobin (24·6–34·8 $\mu\mu$g.) and mean corpuscular hæmoglobin concentration (28·5–37·6%). Clearly increase in diameter parallels increase in mean corpuscular volume but not necessarily mean corpuscular hæmoglobin or mean corpuscular hæmoglobin concentration. This suggests that Bürker's rule, which states that the hæmoglobin content of the red cells is proportional to the surface area, is not valid for normal or for pathological cells.

Department of Physiology,
Airlangga University,
Surabaja, Indonesia. L. M. TJAN HOEN LAY.

EMERGENCY RESUSCITATION IN RUPTURED ECTOPIC GESTATION

SIR,—I was interested in Dr. Azie's letter of Dec. 12. As these cases are always extremely urgent I consider that looking for a compatible donor is a waste of time.

I think that a slight improvement on Dr. Azie's technique, where the facilities are available, is as follows:

When the patient is ready for operation an intravenous plasma or dextrose saline drip is started. When this is working properly it is stopped, because, as Dr. Azie says, it is only diluting the blood and washing red cells into the peritoneum.

The abdomen is then opened and the bleeding stopped in the usual way. A sterile transfusion bottle containing sodium citrate has in the meantime been attached to a sucker. The sucker is turned on and when the bottle is full it is exchanged for the plasma or saline bottle and blood-transfusion is started. Another transfusion bottle is then attached to the sucker. In this way several pints of blood may be collected rapidly for subsequent transfusion when the patient has returned to the ward. A bowl of sterile normal saline is kept handy in case the sucker becomes blocked.

This method has the advantage that less blood is wasted and there is no guddling about with soup ladles, &c.

Cameroons Development Corporation,
Medical Head Office,
Bota/Victoria,
Southern Cameroons. R. F. ANTONIO
Chief Medical Officer.

HIGH PLASMA-IRON IN PORPHYRIA

SIR,—During the course of a survey of Africans with porphyria, we measured the plasma-iron levels in 23 consecutive patients, with the following results:

In 15 cases, the plasma-iron was over 200 μg. per 100 ml., the highest being 345 μg. per 100 ml. (The mean plasma-iron level for normal African subjects in Durban is about 100 μg. per 100 ml.)

2 of the remaining 8 patients had amœbic dysentery, and a 3rd had pulmonary tuberculosis; infections are known to lower plasma-iron values, and this may account for the relatively normal values found in these 3 patients.

Large increases in plasma-iron have, to our knowledge, been reported only in patients with hæmochromatosis and transfusion siderosis,[1] in a proportion of African patients with nutritional siderosis,[2] in infectious hepatitis,[3] in some types of anæmia, and after iron administration.

It would be of interest to know whether other workers have measured plasma-iron in cases with other types of porphyria. If similar high levels have been found, it might throw light on possible relationships between porphyrin biosynthesis and iron metabolism.

University of Natal, and
King Edward VIII Hospital,
Durban. M. HATHORN
N. MCE. LAMONT.

1. Rath, C. E., Finch, C. A. *J. clin. Invest.* 1949, **28**, 79.

THE COST OF DRUG TREATMENT

Sir,—Dr. Harman's report of his impressions derived from "economy committees" are entertaining and no doubt are not meant to be taken seriously. As however his letter has prime place in your columns on Jan. 23 and refers to a serious problem in the economy of the N.H.S., comment from one to whom its conclusions are antipathetic may be justified.

His first generalisation that waste is inevitable is followed by a defeatist recommendation that it had better be accepted. It will be generally admitted that any organisation which aims at efficiency takes steps to limit waste to the minimum, whether it be in the home, big business, or a Government department. In attempting to control extravagant expenditure in drugs the administrator can do little more than issue recommendations unless he interferes unduly with the doctor-patient relationship, and the drug houses cannot be prevented from advertising. On the other hand, the medical practitioner surely can by act and advice exert considerable influence. The cooperation of doctors is the key to the problem, and we should not divest ourselves of the social responsibility though it may not be a matter of direct self-interest. Savings on drug expenditure leave more money for hospital building, more doctors, and more pay for them.

Whether a high drug bill should be a source of national pride is a matter of opinion. Certainly those who doubt the contribution of much drug-taking to what is called the positive health of the nation would not agree to the proposition.

In the last paragraph of Dr. Harman's letter I do not know what is meant by "its own law of growth". Does it derive from Parkinson or Dr. Pangloss? Anyhow I do not think the profession should adopt an attitude of laissez-faire in its approach to the problem at issue.

Selling, Faversham, Kent. MAX PAGE.

SIR,—In their paper of Jan. 2 Dr. Miller and Dr. Smith suggest that distributive costs may account for one-third of the total national drug bill.

This is not unlikely. It should be realised that the cost of most consumer goods increases by at least 50% between leaving farm or factory and their purchase by the consumer (discounting the distorting effects of subsidies, purchase-tax, and similar taxes). Often the increase is far greater.

The cost of distributing drugs in the National Health Service would thus not appear to be excessive in comparison with the cost of distributing other consumer goods.

West Middlesex Hospital,
Isleworth, Middlesex. J. R. SEALE.

SIR,—Of the letters dealing with our paper, I think only that of Dr. Springett calls for a reply. P.A.S. is marketed in many forms, and its basic cost varies by

2. Gillman, T., Lamont, N. McE., Hathorn, M., Canham, P. A. S. *Lancet*, 1957, ii, 173.
3. Peterson, R. E. *J. Lab. clin. Med.* 1952, **39**, 225.

almost 300%. Our figure was based on the price of P.A.S. powders obtaining in July, 1959. Dr. Springett is right in suggesting that the drug is cheaper in tablet form, and where both drugs are prescribed its combination with isoniazid effects a further economy.

Royal Victoria Infirmary,
Newcastle upon Tyne. HENRY MILLER.

INCIDENCE OF ISCHÆMIC HEART-DISEASE AMONG INDIANS IN KENYA

SIR,—So much has been written about the relationship between fat intake and coronary disease that a statistical survey of the disease amongst the various Indian sections in Kenya might prove of value, since these groups vary so greatly in their animal fat consumption.

The Asians, excluding the Goans, may be divided into five main groups:

(1) Gujerati, vegetarians (non-Muslims).
(2) Gujerati, non-vegetarians (mainly Muslims).
(3) Punjabi, vegetarians (non-Muslims).
(4) Punjabi, Sikhs (non-Muslims). (Females usually vegetarian and males non-vegetarian.)
(5) Punjabi, non-vegetarian (Muslims).

The fat consumption rises in this order from (1) to (5), being least in the Gujerati vegetarians and greatest in the Punjabi non-vegetarian Muslims.

TABLE I—NUMBER OF MALE CASES IN EACH GROUP AT DIFFERENT AGES

—	30-39	40-49	50-59	Over 60	Total
Gujerati vegetarians	10	30	44	28	112
Gujerati non-vegetarians	2	17	16	10	45
Total Gujeratis	12	47	60	38	157
Punjabi vegetarians	4	11	18	8	41
Punjabi non-vegetarian Sikhs	1	9	12	10	32
Punjabi non-vegetarian Muslims	2	8	10	6	26
Total Punjabi non-vegetarians	3	17	22	16	58
Total Punjabis	7	28	40	24	99
Total Indians	19	75	100	62	256
Goans	1	14	14	14	43

The population figures have been calculated from the census for 1948,[1] according to which males over the age of 15 number 29,000 Indians and 3000 Goans. The Asian population, it is estimated, increased by $2^1/_2$% per annum since that year, but the proportion between the various groups has remained about the same.[2] Muslims form 31% and non-Muslims 69% of the Indian population, Muslims thus comprising 9000 and non-Muslims 20,000 males over the age of 15. Hindu males at the same age number 15,000 and Sikhs 3000. Further assessments have been obtained by inquiry from electoral candidates who subdivide their electorates in order to estimate their supporters who come mainly from their own communities; in this way it has been calculated that Gujerati Hindus (vegetarians) outnumber Punjabi vegetarians by about 2 to 1, and that Gujerati Muslims (non-vegetarians) exceed Punjabi Muslims by the same proportion. The relative figures of these groups for males over the age of 15 are Gujerati vegetarians 10,000, Punjabi vegetarians 5000, Gujerati Muslims 6000, and Punjabi Muslims 3000.

The male Indian population of Kenya over the age of 15 therefore includes the following main groups:

Gujerati vegetarians (Hindus)	10,000
Gujerati non-vegetarians (Muslims)	6000
Total Gujeratis	16,000
Punjabi vegetarians (Hindus)	5000
Punjabi non-vegetarian Sikhs	3000
Punjabi non-vegetarian Muslims	3000
Total Punjabi non-vegetarians	6000
Total Punjabis	11,000
Total Indians in these groups	27,000

Our series consists of 320 consecutive cases of ischæmic heart-disease seen in Kenya during the past thirteen years, including 170 Gujeratis, 104 Punjabis, and 46 Goans. All the diagnoses were confirmed clinically and electrocardiographically by one of us. Necropsy in fatal cases was never possible, since Indians in Kenya never allow postmortem examinations on their relatives. All were men with the exception of 21 women (18 Indians and 3 Goans).

A comparison between the 153 vegetarian and the 103 non-vegetarian males showed that hypertension was slightly more frequent (30%) amongst vegetarians than non-vegetarians (25%) and that diabetes had approximately the same incidence (13% and 15%) in the two groups. The total Gujeratis and total Punjabis displayed almost the same proportions of each disease.

The ages of the male patients in the various communities are given in table I, which reveals that the incidence of coronary disease is highest in the sixth decade.

The standard daily diets of the main Indian groups [3] are listed in table II. According to Adalja,[2] the average consumption of milk and ghee has fallen by about 30% since 1927, partly because more tea, and correspondingly less milk, is taken, and partly because these substances were thought to give protection against malaria and pneumonia before the advances of chemotherapy. There has also been a tendency since the end of the late war for a few of the vegetarians to be less strict in their diet, particularly when they go out to meals with members of other communities.

The incidence of ischæmic heart-disease in relation to Kenya population in the different groups, is depicted in table III.

TABLE II—STANDARD DAILY DIETS OF EACH GROUP

Item	Gujerati veg.	Gujerati non-veg.	Punjabi veg.	Punjabi non-veg.
Atta	10 oz.	9 oz.	14 oz.	12 oz.
Rice	3 oz.	3 oz.	1 oz.	2 oz.
Dhall	2 oz.	2 oz.	3 oz.	2 oz.
Vegetables	8 oz.	6 oz.	8 oz.	6 oz.
Sugar	3 oz.	3 oz.	3 oz.	3 oz.
Meat	Nil	4 oz.	Nil	5 oz.
Eggs	Nil	1	Nil	1
Milk	6 oz.	6 oz.	12 oz.	12 oz.
Ghee	2 oz.	2 oz.	$3^1/_2$ oz.	$3^1/_2$ oz.
Vegetable oil	$1^1/_2$ oz.	$1^1/_2$ oz.	Nil	Nil

Atta is coarsely ground wheat flour, plus 15% bran. Dhall is the pigeon pea, *Cajanus indicus*. Vegetable oils, which are prepared locally, include simsim oil, which is made from millet, groundnut oil, and cottonseed oil, none of which are hydrogenated.

The figures for milk in the original table have been altered to conform with the average adult consumption at the present time.

TABLE III—INCIDENCE OF ISCHÆMIC HEART-DISEASE IN MEN IN RELATION TO MALE POPULATION OVER THE AGE OF 15

—	No. of cases	% of total Indian cases	Kenya population (approx.)	Population % of total Indians
Gujerati vegetarians	112	44	10,000	37
Gujerati non-veg.	45	17	6000	22
Total Gujeratis	157	61	16,000	59
Punjabi vegetarians	41	16	5000	19
Punjabi non-veg. Sikhs	32	13	3000	11
Punjabi non-veg. Muslims	26	10	3000	11
Total Punjabi non-veg.	58	23	6000	22
Total Punjabis	99	39	11,000	41
Total Indians	256		27,000	

For the sake of accurate comparison females have been excluded because they form such a small proportion of the coronary cases and because the sexes of the Sikh community differ in their diet, females being predominantly vegetarian whereas males are usually non-vegetarian. Since the Statistical Abstract [1] gives no separate figures for population between the ages of 15 and 60, the estimates in this table comprise males over the age of 15.

The ratio between percentage incidence of ischæmic heart-disease and percentage of population is almost identical in the total Gujeratis and total Punjabis, the percentage coronary moribidity in each case being closely proportional to that of population, in spite of the fact that the Gujeratis are the lowest and the Punjabis the highest fat consumers. These statistics suggest, therefore,

1. Statistical Abstract, East African Statistical Department, Kenya Unit, 1958.
2. Adalja, K. V. Personal communication, 1959.
3. Harvey, D. *East Afr. med. J.* 1943, **20**, 235.

that, as was hinted by Adalja,[4] in the case of Indians in Kenya the ingestion of animal fats is not an important ætiological factor. Another point of interest is that the amount of vegetable oils, such as simsim, groundnut, and cottonseed oils, which are not hydrogenated, tends to be consumed in inverse ratio to that of animal fats. It thus seems that the Gujerati vegetarians were not protected from coronary occlusion by a high intake of unsaturated fatty acids.

Smoking does not seem to be an important factor since Sikhs, who never smoke, show approximately the same incidence of ischæmic heart-disease in relation to their population as the other Punjabis and total Gujeratis, amongst whom smoking is practised by most Indian males over the age of 25.

We consider that further research into the comparative incidence of coronary occlusion amongst the various Asian communities in Kenya, analysis of their diets, and counting of their populations might throw more light upon the ætiology of the disease.

We wish to express our gratitude to the Hon. Dr. K. V. Adalja for his valuable assistance in classifying the various Indian groups and in providing particulars concerning their population and diet. We are also grateful to the doctors who referred their cases to us.

Nairobi, Kenya.

A. D. CHARTERS
B. P. ARYA.

HOTELS OR HOSPITALS?

SIR,—I have read Mr. Stallworthy's article of Jan. 9 with great interest. Experience of the operation of convalescent annexes or halfway houses attached to geriatric units supports his suggestion that the provision of these annexes for other medical units would be of value. A number of halfway houses have been established by the King Edward's Hospital Fund for London and by the National Corporation for the Care of Old People, and my observations are based on the working of the home attached to the geriatric unit of the Whittington Hospital during the past nine years.

The adverse psychological effects of prolonged stay of geriatric patients in the hospital ward are well recognised. Apart from apathy and personality deterioration many patients, lacking incentive, become dependent on the services of the nursing staff. Whereas what is needed is encouragement for the patient to become independent after the acute phase of his illness has been treated. Independence is often more easily achieved in the halfway house than in the hospital ward. One of the most important functions of the halfway house is to provide facilities for further rehabilitation and thus shorten the length of stay in hospital. The patient with hemiplegia, for example, may have recovered sufficiently in hospital to be able to walk, but because he cannot dress himself or manage stairs he is still dependent on help from others. He can learn to perform these activities in the halfway house where a marked improvement in morale and speed of recovery is often noticed as confidence and interest in living are renewed. Hemiplegic patients whose recovery was satisfactory spent on the average 7 weeks in the geriatric unit and a further 5 weeks in the halfway house before returning to an independent existence at home.

Another important advantage of the recovery annexe or halfway house is that the patient's physical and mental capabilities can be more easily assessed there than in the hospital ward. Thus the patient is not discharged home until it is reasonably certain that he or she is capable of managing at home. As a result premature readmission to hospital can be avoided. Adams [5] found that with the availability of the beds in Seapark, a recovery home attached to the Belfast Geriatric Unit, the readmission-rate in 1953 fell from its usual level of 12% to 8%.

The possible dangers of loss of continuity of care mentioned by Mr. Sanford (Jan. 23) are not present in the case of the halfway house whose operation I have observed. But continued regular visits by the hospital consultant and by the almoner are essential. As far as possible the plan for the patient's further care is decided upon before he is transferred from hospital to the annexe. The successful operation of halfway houses at present in existence, their undisputed value to geriatric units, and the substantial contribution they make to the recovery of many elderly patients indicate the need for similar homes attached to other medical units which are treating an ever-increasing proportion of patients in the older age-groups.

Whittington Hospital, London, N.19. A. N. EXTON-SMITH.

4. Adalja, K. V. Kenya Faculty of the College of General Practitioners, London, Oct. 4, 1958.
5. Adams, G. F. *Lancet*, 1954, ii, 486.

FIBRINOLYTIC ACTIVITY OF BLOOD IN INTERMITTENT CLAUDICATION

SIR,—We were interested to read Dr. Nestel's paper of Sept. 19, in which he says that deficient fibrinolysis has been previously demonstrated only in acute episodes, as in coronary occlusion. In this clinic, the fibrinolytic activity was measured in thromboangiitis obliterans, arteriosclerosis obliterans, and atherosclerosis.

Fibrinolysis in the euglobulins was depressed in 6 out of 24 cases of arteriosclerosis obliterans and in 4 out of 21 cases of thromboangiitis obliterans. In 100 patients with atherosclerosis there was a tendency to deficient fibrinolysis in the euglobulins and a statistically important prolongation of fibrinolysis time of total plasma activated with streptokinase. No changes in plasminogen activity were found. A possible relation of these findings to the antifibrinolytic activity was considered.

The results [1] were given to the XIX Congress of the Polish Internists Association in Poznań in September, 1957, and to the XX Congress in Gdańsk last September. The problem of fibrinolysis in atherosclerosis was also discussed by other Polish authors (E. Szczeklik et al. and H. W. Gajewski).

I Medical Clinic, Warsaw Medical Academy. WINCENTY CZARNIECKI.

ANABOLIC STEROIDS AND RADIATION DAMAGE

SIR,—Szold et al.[2] and Fehér et al.[3] demonstrated significantly higher survival-rates in nephrectomised uræmic animals treated with an anabolic agent, 19-norandrostenolone phenylpropionate ('Durabolin') than in controls. The uræmic state has many similarities to acute radiation sickness, and the idea was thus raised that acute radiation damage might be retarded or prevented by anabolic agents.

Adult male rats were given a total-body dose of 1000r (180 kV, 6 mA, 2·5 Al filter, 50 cm. focus-skin distance, the dose controlled with a Siemens-Universal dosimeter). The animals to be protected were given, at the onset daily, later on every second day, 0·5 mg. of 19-norandrostenolone phenylpropionate, and the controls received the same amount of physiological saline.

From the second day after irradiation the clinical appearance of the animals became very similar to that of rats with arenal uræmia, with the difference that the symptoms of the protected animals were significantly less. The protected animals were fresher, responded better to external stimuli, were curious, and had a better appetite. Before they died all became restless and dragged their hind limbs which were subject to convulsive spasms.

1. *Polskie Archiwum Medycyny Wewnętrznej*, 1958, **12**, 1569.
2. Szold, E., Szendrői, Z., Weisz, P., Pintér, I., Dési, I., Kádas, T. *Lancet*, 1959, i, 368.
3. Fehér, I., Dési, I., Szold, E. *Magyar Tudományos Akadémia V. oszt. Közleményei*, 1958, **9**, no. 3-4.

After the third day both groups showed a distinct reduction in temperature and weight, and these changes were accompanied by diarrhœa for two or three days.

The five series (taking into consideration the first 10 days) showed a significant 40% difference in survival in favour of the protected animals.

By the fortieth day the protected animals and the controls showed practically no difference in survival. A protected and a control animal of two series were killed and their organs examined. Histologically the testicles of the controls showed severe degenerative changes, whereas in the protected animals there were well-recognisable testicular ducts, good nuclear staining, and even spermatogenesis here and there.

Our observations so far and the difference in the histological appearance of the testes give reason to extend these experiments on a larger scale.

E. SZOLD
B. GIMES
B. ERDÖS.

Roentgenological and Urological Clinics,
University Medical School, Budapest.

A NEW STEROID IN THE URINE IN NEPHROSIS

SIR,—In the course of steroid estimations a new reducing substance which behaves chromatographically like a corticosteroid has been found in the urine of untreated nephrotic patients.

After 24 hours of mild acid hydrolysis at pH 1, the urines of 8 nephrotic children were extracted with chloroform. After extraction the urines were incubated at pH 4·5 with 25 units per ml. of calf-spleen glucuronidase for 48 hours, and again extracted with chloroform. To purify them, the fractions were partitioned between benzene and water. The materials from the watery phase were then run on paper in Bush's C chromatographic system [1] at room temperature.

On spraying the paper with alkaline tetrazolium-blue solution, we found a reducing substance with R_f value of 0·58 (corresponding R_f values are: hydrocortisone 0·3, cortisone 0·44, 11-desoxy-17-hydroxycorticosterone 0·65, corticosterone 0·75). The substance eluted from the paper was then acetylated and rerun in a system of hexan/benzene/methanol/water 4 : 1 : 4 : 1. The R_f value of the acetate was 0·29 (corresponding values: hydrocortisone acetate 0·05, cortisone acetate 0·11, 11-desoxy-17-hydroxycorticosterone acetate 0·08, corticosterone acetate 0·07, aldosterone-21-monoacetate 0·07, aldosterone-18,21-diacetate 0·21).

The substance gives a positive soda-fluorescence test indicating the presence of a Δ^4-3-keto group, and it is Porter-Silber negative, therefore does not contain a hydroxyl group on C_{17}. The prompt reaction to tetrazolium-blue suggests the presence of a ketol rather than a glycol side-chain; and the relatively high R_f value of the acetate suggests a diacetate form. The substance is not identical with Nowaczynski's compound III.[2] Its identity with Pasqualini's compound has not been investigated.[3]

This steroid could not be demonstrated in nephrotic urine by only mild acid hydrolysis; nor could it be seen in the urine of healthy children even though it was subjected to hydrolysis with glucuronidase. After suppression of the secretory activity of the patients' adrenals with prednisone or prednisolone, the substance disappeared from the urine in 4 cases studied.

The purpose of our future investigations will be a more precise identification of this steroid and observation of the changes in excretion of the substance at different stages of this and other diseases.

J. CSORDÁS
P. JOBST
P. CHOLNOKY.

Children's Clinic,
University of Pécs, Hungary.

1. Bush, I. E. *Biochem. J.* 1952, **50**, 370.
2. Nowaczynski, W., Steyermark, P. R., Koiw, E., Genest, J., Jones, R. W. *Canad. J. Biochem.* 1956, **34**, 1023.
3. Pasqualini, J. *C.R. Acad. Sci., Paris*, 1958, **247**, 1061.

PREVENTION OF MIGRAINE IN CHILDREN BY PROCHLORPERAZINE

Dr. NEVIL LEYTON writes:

"Contrary to what Professor Illingworth and Dr. Harvey imply in their article of Jan. 16, I have never made any claim that 'Stemetil' alone is particularly useful in the prevention of migraine. Indeed, I said [1] 'many patients whom I have treated with it have either been unaffected or their headaches made worse, although I am glad to say that some have benefited'. The conclusions Professor Illingworth and Dr. Harvey have reached simply confirm my own.

"It has always been my opinion that no one scheme, and certainly no compound, will ever be of universal use in preventing attacks of migraine. The compound which I have found most consistently of use, particularly when assisted by others, is chorionic gonadotrophin.[2]"

1. Leyton N. *Lancet*, 1957, ii, 242.
2. Leyton, N. *ibid.* 1942, i, 448.

Parliament

The Scottish Mental Health Bill

IN Scotland the law relating to mental health differs in many ways from English practice. Its revision was considered by the Russell Committee which reported in 1946 [3] and a white-paper setting out proposals for its amendments was published in 1955.[4] Action was deferred until the English Royal Commission should report, and the Secretary of State for Scotland then invited the Scottish Health Services Council to consider the application of the Commission's main recommendations to Scotland. The council has published two reports [5] from the committee which they set up for this purpose. The Mental Health (Scotland) Bill, which has been prepared against this background, will have its second reading soon after Parliament reassembles. Its main provisions are described in a white-paper [6] published by the Department of Health for Scotland.

The Bill accepts most of the recommendations of the English Royal Commission—notably, that mental patients should have access to care and treatment without formality; that compulsion should be reduced to a minimum; and that the community mental-health services should be developed.

In three important respects, however, the Scottish Bill departs from the English legislative pattern. Throughout "mental disorder" is used as a general term to cover mental illness and mental deficiency and these are the only categories mentioned in the Bill.

The Bill dissolves the General Board of Control for Scotland, but sets up in its place a Mental Welfare Board which will continue to carry out the old board's protective functions by investigating complaints and visiting patients in hospital or under guardianship. The board will have not fewer than 5 members and not more than 7, of whom at least 2 must be doctors.

The Bill also retains the services of the sheriff, a traditional Scottish legal officer who has no exact English counterpart. Thus the sheriff must approve applications for compulsory admission (which must be signed by two doctors). The patient, or his nearest relative, has also the right of appeal to the sheriff against continued detention. This procedure will take the place of the new appeal tribunals to be set up under the English Bill.

The Scottish Bill places a specific duty (not provided under the present law) on the doctor in charge of the patient to discharge him if he no longer needs to be detained. A similar duty is also placed on the new Mental Welfare Board. (The nearest relative, or the hospital board or local authority concerned, may also discharge a patient.) Courts will for the first time be given the power to remand in hospital instead of in custody people who seem to be mentally disordered.

3. See *ibid.* 1946, ii, 166.
4. *ibid.* 1955, ii, 1983.
5. *ibid.* 1958, ii, 741.
6. H.M. Stationery Office. 1960. Pp. 15. 1s.

Notes and News

WORLD HEALTH ORGANISATION

ON Jan. 19 the Executive Board of W.H.O. met in Geneva under the chairmanship of Prof. E. Aujaleu, director-general of public health, France. By the end of November about 11½ million dollars had been contributed to W.H.O.'s malaria eradication campaign. A further 8½ million dollars is needed to finance W.H.O.'s malaria commitments up to the end of 1961.

The canton of Geneva has now designated the property which it will place at the disposal of W.H.O. for its new building, while the Swiss Parliament has authorised an interest-free loan to W.H.O. of 20 million Swiss francs, repayable in twenty annuities.

The regular working budget of the Organisation proposed for 1961 is 18½ million dollars.

HINCHLIFFE RECOMMENDATIONS

THE Ministry of Health has been considering the report of the Hinchliffe Committee, and, with the agreement of the General Medical Services Committee, has commended to general practitioners (ECN 319) the recommendation that they should restrict the quantities of drugs they prescribe. The Committee suggested that normally, except for chronic patients, the amount of drugs to be ordered on one prescription should not exceed one week's supply. Other recommendations which the Ministry commends are that official titles should be used on prescriptions in preference to proprietary names, and that practitioners should avoid prescribing unnecessarily elaborate preparations. The Committee's suggestion that new drugs should not be used in the National Health Service until they have undergone independent clinical trials is under consideration. Meantime doctors are asked, until the results of trials are known, to prescribe new drugs only if they are sure that existing drugs have failed. It has been agreed with the professional bodies to produce a looseleaf handbook including much of the British *National Formulary* and facts about comparative costs of standard and proprietary preparations, and it is hoped to circulate copies to general practitioners soon. The value of pre- and post-graduate training and education in prescribing is also stressed, especially arrangements for seconding medical students to general practitioners, refresher courses for practitioners, and the trainee practitioner scheme.

MALNUTRITION IN AFRICA

AT Dar-es-Salaam on Jan. 13, opening a scientific conference on the Origin and Effects of Malnutrition in Man and Animals, Sir Richard Turnbull, the Governor of Tanganyika, gave highest priority to studies connected with infant mortality and infant malnutrition in the hope of removing "those heavy handicaps of stunted physical growth and impaired intellectual development which so often result from early deficiencies in diet". Enormous areas of Tanganyika, he said, were infested with tsetse and as a result stock-farming in about two-thirds of the country was impossible. The people living in and behind the fly areas suffered from a general protein deficiency, and he wanted to know whether this could be made good from vegetable sources alone and without reliance upon milk in any form.

"I feel that if we are to find a solution to this problem and not just a palliative, it must come from local resources; we cannot afford to be dependent on a supply of milk or some kind of animal protein concentrate from outside as a supplement to the diet."

Prof. B. S. Platt, in his presidential address, said that twenty years ago there was much talk of the "lazy African"—often coupled with talk about the need for incentives for him to better his lot.

"I have always tended to associate indolence with ill-health. When I first visited East Africa in 1938, I had fresh in my mind the contrast between the listless and apathetic, poorly fed apprentices in small factories in Shanghai and the noisy, mischievous and high-spirited ones who were well fed from a kitchen run under my supervision, and I found a similar contrast between groups of well and badly fed labourers in the goldfields in Tanganyika."

The morphological changes found in the central nervous system in animals in experimental malnutrition might, Professor Platt thought, have some relevance to certain mental disturbances in malnourished human beings.

HOSPITAL MICROCOSM

MANY doctors who read the *Graver Tribe* were left with a feeling that they had involuntarily acquired a second medical school. Those who have been awaiting further news about St. Chad's will turn to Edward Candy's new book [1] to catch up with the gossip of what must surely be the wittiest and most civilised hospital in London. Nor will they be disappointed. Within a few pages they will be *au fait* with the tussle for the old eye and tubercle wards on the top floor of the surgical block, alert to find out whether Clayton will successfully commandeer them for his burns unit or whether they will be given to Branksome as a temporary surgical home till his new unit is built.

One of the reasons why we are so much absorbed by St. Chad's is that the staff and their womenfolk, the patients and their relatives, show the same maddening mixture of good and bad, strength and weakness, generosity and meanness as our own friends or even ourselves. This time Mr. Candy has been content to avoid the interruption of near-melodrama and leaves us to follow the much more exciting manœuvre in committee, exchange at the hospital dance, or row in out-patients. But the everyday never lapses into the trivial, for he recognises the universal issues behind the humdrum, respects diverse but sincere principles, and offers his own implicit, though never explicit, judgments.

University of London

The following degrees have been awarded:

M.D.—John Burston, A. M. Dawson, P. J. Koblenzer, A. C. K. Lawrence, Ian Macdonald, J. D. Pryce.

Ph.D. (in the faculty of medicine).—Krishna Rao Voommaji Rao Ghorpade.

University of Aberdeen

Dr. I. B. Porteous has been appointed a lecturer in pathology.

University of Glasgow

The Bellahouston medals for 1959 have been awarded to W. A. J. Crane, James Crooks, and A. J. S. McFadzean.

On Jan. 16 the degrees of M.B., CH.B. were conferred on Yuill Black (in absentia).

Monash University

Dr. A. J. Marshall has been appointed professor of biology at this new university in Victoria, Australia.

University College Hospital

Prof. Montague Maizels will give the Sydney Ringer lecture at the Medical School, University Street, London, W.C.1, on Tuesday, March 15, at 4.30 P.M. He will speak on salt and water balance in cells.

World Health Day

The theme chosen for World Health Day for 1960 is Malaria Eradication—a World Challenge. It will be held as usual on April 7.

Partnership in Preventive Medicine

The Society of Medical Officers of Health and the College of General Practitioners will hold a postgraduate conference on July 16 and 17, at the medical school, University of Birmingham. Further particulars will be given later.

North of England Obstetrical and Gynæcological Society

The following officers have been elected for 1960:

President, Prof. T. N. A. Jeffcoate; vice-presidents, Mr. J. B. Farquhar, Sir Arthur Gemmell, Miss E. M. Mills, Mr. J. M. King, Mr. J. A. Hadley; hon. treasurer, Mr. T. B. FitzGerald; hon. general secretary, Mr. H. V. Corbett; hon. reporting secretary, Miss U. M. Lister.

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1. A Lady's Hand. By EDWARD CANDY. London: Gollancz. 1959. Pp. 192. 13*s.* 6*d.*

International Conference on Medical Electronics

This conference will be held at Olympia, London, from July 21 to 27. Further particulars may be had from the conference secretariat, Institution of Electrical Engineers, Savoy Place, W.C.2.

European Congress on Aviation Medicine

This congress will be held in London from Aug. 29 to Sept. 2. Further particulars may be had from the congress secretary, c/o British European Airways, Central Medical Clinic, London Airport (N), Hounslow, Middlesex.

Rehabilitation of the Amputee

A course for orthopædic consultants and senior registrars will be held from March 28 to April 1 at the Limb Fitting Centre, Queen Mary's Hospital, Roehampton, London, S.W.15. Applications should be sent to the Principal Medical Officer, Artificial Limbs and Appliances (Med. 5 PL) at the same address.

Prof. A. D. Macdonald, president of the British section of the Franco-British Pharmaceutical Commission, has been appointed an officer of the Ordre de la Santé Publique by the French Minister of Health.

The Yorkshire Society of Anæsthetists will hold their annual general meeting on Wednesday, Feb. 10, at 8.30 P.M. at the General Infirmary at Leeds. Dr. W. J. Finnie will give his presidential address on the training and distribution of anæsthetists.

The Group for Representation of the Views of Clinical Psychiatrists will meet on Tuesday, Feb. 16, at 5.30 P.M., at Tavistock House North, London, W.C.1. The secretary of this group is Dr. B. C. Gilsenan, Shenley Hospital, near St. Albans, Herts.

The National Institutes of Health have published a bibliography (*Publ. Hlth Serv. Publ.* no. 669) of papers published in English during 1952–58 about the effect on the offspring of the following disorders in the mother: infectious diseases, diabetes, thyroid dysfunction, myasthenia gravis, lupus erythematosus, sickle-cell disease, thrombocytopenic purpura, leukæmia, drug addiction, and drug administration. Statistical studies of perinatal morbidity and mortality are also included. A limited number of copies are available from the library of the Institutes, Bethesda 14, Maryland. Additional copies may be purchased from the Government Printing Office, Washington 25, D.C. (15 cents per copy).

Boarding-out Schemes for Elderly People.—Copies of this booklet (1*s.* 6*d.*) may be had from the National Council of Social Service (26, Bedford Square, London, W.C.1). It offers advice on how to run a boarding-out scheme and includes a brief survey of information drawn from existing schemes sponsored by voluntary bodies and local authorities.

'Versenate', mentioned in the paper by Dr. Miller and Dr. Smith (Jan. 2), is a trade mark of the Dow Chemical Co., and Riker Laboratories Ltd. are registered users.

Appointments

CHYNOWETH, ALAN, M.R.C.S.: assistant M.O.H. and school M.O., Derbyshire.
EUSTACE, MURIEL M., L.R.C.P.I.: school M.O., Co. Durham.
HOWARTH, BESSIE, M.B. Lpool: assistant divisional M.O., Lancashire (Golbourne area).
JOHNSON, WILLIAM, M.R.C.S.: senior M.O. for mental health, Staffordshire.
LINFOOT, C. W., M.B. Durh: senior casualty officer (medical), Newcastle upon Tyne group of hospitals.
MURPHY, M. I., M.B., D.P.H.: school M.O. and assistant M.O.H., Leicester.
PEPPER, M., M.B. Lond.: school M.O. and assistant M.O.H., Leicester.

East Anglian Regional Hospital Board:

BOYD, R. V., M.B. Lond., D.C.H.: registrar in geriatrics, Ipswich and East Suffolk hospital group.
DEW-JONES, J. A., M.R.C.S.: senior registrar in psychiatry, St. Andrew's Hospital, Norwich.
HARRIS, W. G., M.B. Lond.: surgical registrar, Ipswich and East Suffolk Hospital.
HODGSON, O. E. F., M.B. Cantab., D.P.M.: consultant psychiatrist, Fulbourn and Addenbrooke's Hospitals.
JADHAV, N. A., M.B. Mysore, M.R.C.P.E.: medical registrar, North Cambridgeshire and Clarkson Hospitals, Wisbech.
JENKINSON, JANE G., M.B. Lond., D.C.H.: pædiatric registrar, Ipswich and East Suffolk Hospital.
LAWRENCE, G. A., M.B. Lond., F.R.C.S.E.: surgical registrar, Norfolk and Norwich Hospital.
SINGH, P., M.B. Lucknow, M.R.C.P.: medical registrar, West Suffolk General Hospital.
SKORBINSKI, A. W., M.B. Cape Town: surgical registrar, Peterborough Memorial Hospital.
SMITH, B. A. M., M.B. Leeds, D.C.H.: pædiatric registrar, Peterborough group of hospitals.
SUKUMAR, I. P., M.B. Madras: medical registrar, Papworth Hospital.

Diary of the Week

JAN. 31 TO FEB. 6

Monday, 1st

GUY'S HOSPITAL, S.E.1.
5.30 P.M. Dr. Oliver Garrod, Dr. I. H. Mills: Aldosterone Metabolism.
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Mr. N. W. Please: Elements of Statistical Methods.

Tuesday, 2nd

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Dr. L. G. Norman: Medical Aspects of the Prevention of Road Accidents. (First of two Milroy lectures.)
ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. A. H. C. Ratliff: Fractures of the Femoral Neck in Children. (Hunterian lecture.)
UNIVERSITY OF LONDON
5.30 P.M. (Middlesex Hospital Medical School, Mortimer Street, W.1.) Dr. Honor B. Fell: Experimental Transformation of Cells.
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Pathology and Medicine.* Prof. Alan Kekwick, Prof. J. W. S. Blacklock, Dr. R. R. Wilson: The Pathologist and the Patient.
8.30 P.M. *Orthopædics.* Mr. David Trevor: Treatment of Congenital Dysplasia of the Hip in Older Children. (Presidential address.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. Paul Fourman: Magnesium Metabolism in Man.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Mr. J. G. Dumoulin: Fœtal Distress.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Dr. H. C. Grant: Pathology of the Dementias.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. P. J. Hare: Coccal Infections.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. Denis Hill: E.E.G. Diagnosis of the Epileptogenic Focus.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Prof. Adam Patrick: Herpes Zoster.

Wednesday, 3rd

ROYAL SOCIETY OF MEDICINE
5.15 P.M. *History of Medicine.* Dr. J. F. E. Bloss: History of Sleeping Sickness in the Sudan.
8 P.M. *Surgery.* Mr. Rodney Maingot: Surgical Aspects of Non-malignant Stricture of the Bile Duct with Special Reference to Postoperative Strictures. (Presidential address.)
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Henry Haber: Rare Tumours of the Skin.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. W. E. Lloyd: Observations on Round Foci.
ASSURANCE MEDICAL SOCIETY
5 P.M. (11, Chandos Street, W.1.) Discussion: Doubtful Cases.
MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (18, Nicolson Street, Edinburgh.) Prof. G. L. Montgomery: Observations on the Pathology of the Myocardium.
UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Queen's College, Dundee.) Dr. F. L. Mitchell, Prof. R. B. Hunter: Methods of Investigation of Adrenal Cortical Function.

Thursday, 4th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M. Dr. Norman: Medical Aspects of the Prevention of Road Accidents. (Last of two Milroy lectures.)
ROYAL COLLEGE OF SURGEONS OF ENGLAND
5.30 P.M. Prof. T. Pomfret Kilner: Plastic Surgery of the Upper Jaw.
ROYAL SOCIETY OF MEDICINE
8 P.M. *Neurology.* Mr. D. W. C. Northfield, Dr. G. F. Swann, Dr. James Bull: Development in Contrast Radiography.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof. E. B. Verney: Aspects of the Renal Excretion of Water and Electrolytes.
UNIVERSITY COLLEGE, Gower Street, W.1
5 P.M. Dr. Elizabeth Work: The Mucopeptides of Bacterial Cell Walls. (First of two lectures.)
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Dr. E. M. McGirr: Development of Knowledge of the Ætiology of Goitre.

Friday, 5th

UNIVERSITY OF LONDON
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof. Heinrich Pette (Hamburg): Experimental Demyelinating Diseases and Their Implications in Neurological Diseases of Man.
ROYAL SOCIETY OF MEDICINE
2.30 P.M. *Laryngology.* Mr. Ivor Frew, Dr. E. A. Cooper: Tracheostomy and Controlled Respiration.
5.30 P.M. *Anæsthetics.* Dr. John Bullough: Obstetric Analgesia Based on Pethidine/Antagonist Mixtures.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Sir Russell Brock: Basic Principles in Cardiac Surgery.
4 P.M. Mr. Please: Elements of Statistical Methods.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Mr. G. H. Howells: Cancer of the Larynx.
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
4 P.M. Dr. J. Purdon Martin: Observations on Involuntary Movements and Tremor.

Saturday, 6th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
NOON. Dr. Roger Maspétiol (Paris): Factors of Success in Tympanoplasty.
MIDLAND THORACIC SOCIETY
3 P.M. (36, Harborne Road, Edgbaston, Birmingham, 15.) Prof. W. Melville Arnott: Management of Cardiac Failure.